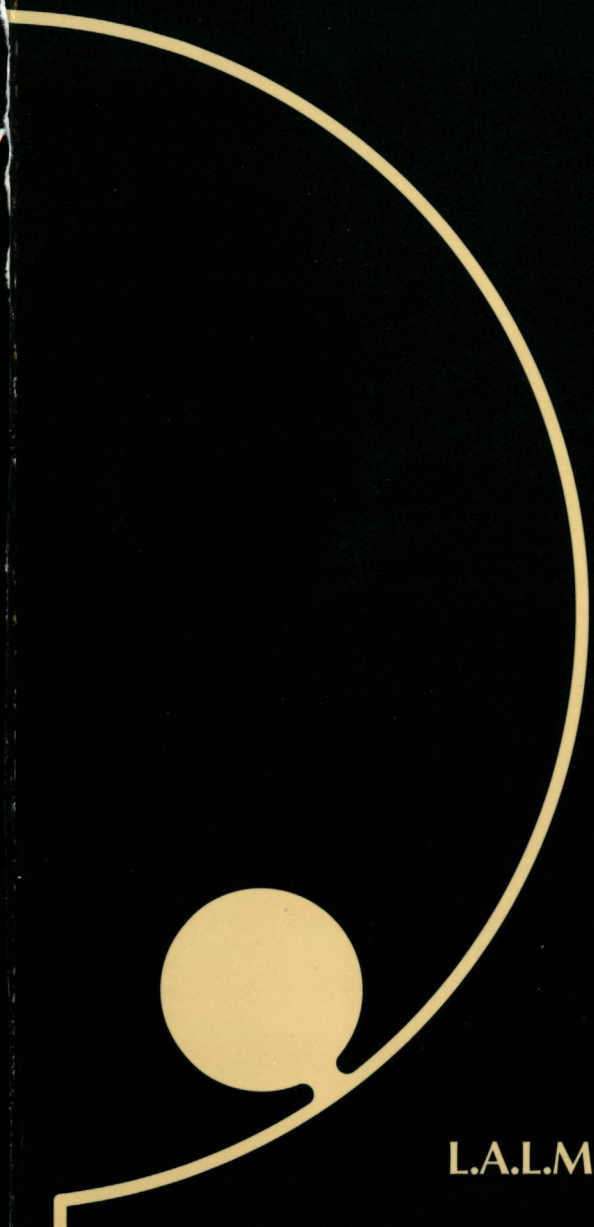
PROGNOSTIC ASSESSMENT IN SUPERFICIAL BLADDER CANCER



L.A.L.M. KIEMENEY

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PROGNOSTIC ASSESSMENT IN SUPERFICIAL BLADDER CANCER

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Voor Jan en Lies

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CHAPTER 1

INTRODUCTION

BLADDER CANCER OCCURRENCE

Among the 15 million inhabitants of the Netherlands, approximately 2700 new cases of bladder cancer are diagnosed each year in men and 700 in women.[11] After lung cancer and prostate cancer, it is the third most frequently occurring tumour in men. Approximately 800 and 300 Dutch men and women die from the disease each year, respectively.[3]

In most Western communities, bladder cancer incidence and mortality rates are still increasing, although these increasing trends seem to have leveled off in males over the past few years.[17] The latter observation may be explained by the fact that an increasing proportion of male Western populations are life-long non-smokers. It is possible that the introduction of various new classification and registration procedures for low-stage bladder cancer since the 1970s have biased the interpretation of these trends in incidence.[12,15] Since the implementation of the WHO grading system in 1973,[13] the controversial opinions concerning the most appropriate nomenclature for low-grade papillary lesions of the urinary bladder have swung firmly in favour of considering the great majority of these lesions to be malignant.[5]

SUPERFICIAL BLADDER CANCER

The majority (approximately 65 per cent) of newly diagnosed bladder cancers are low-stage, or 'superficial', transitional cell carcinomas (TCC).[4] Superficial is defined as tumour extension limited to the mucosa (flat pTis and papillary shaped pTa tumours) or the lamina propria (pT1) of the bladder wall.[18] Even though, strictly speaking, pT1 tumours show invasion beyond the basal layer of the urothelium, in urology practice only the muscle-invasive pT2-pT4 tumo urs are actually called 'invasive'. This difference between the official TNM definition of invasiveness and the definition used in urological practice, is caus ed by the clear differences in prognosis and management policy for superficial and invasive bladder cancer. Whereas invasive bladder cancer is routinely treated with cystectomy, radiotherapy or a combination of these two modalities with or without upfront chemotherapy, superficial tumours are managed more conservatively by transurethral resection (TUR), which may be followed by intravesical instillations with chemotherapeutical or immunotherapeutical agents.[14]

PROGNOSIS

Patients diagnosed with superficial bladder cancer have a relatively good prognosis *quoad vitam* and are therefore treated conservatively. Nevertheless, there is a strong tendency for new tumours to form after initial surgery. Approximately 60 per cent of all the patients suffer at least one recurrence

within five years of the initial diagnosis.[4,8] Many patients experience multiple recurrences, necessitating repeated resections or fulguration. Additional measures are required, however, if recurrent tumours show muscle invasion and/or appear to be poorly differentiated. In 10 to 30 per cent of all the patients with primary superficial TCC, sooner or later such progressive tumour behaviour is observed.[9] Because of disease progression, it is estimated that 10-15 per cent of all the patients who initially present with a superficial tumour die from bladder cancer within five years of the first TUR.[2,7] At least in theory, the administration of more aggressive treatment could prevent bladder cancer death in some of these 'high risk' patients. It is very important therefore to identify patients with a poor prognosis at the earliest possible stage.

PROGNOSTIC FACTORS

The major prognostic factors for recurrent tumour formation and disease progression in superficial TCC are tumour stage, degree of differentiation, size and multicentricity. Once a patient has suffered a recurrence, he or she is prone to having more recurrences.[1,4,8] Despite the presence of these prognosticators, it is the urologist's experience that superficial bladder cancer is a heterogeneous disease with a rather unpredictable clinical course. Therefore, current research is aimed at identifying more powerful prognosticators, especially for disease progression. For example, much work has focused on identifying chromosomal and DNA content differences between urothelial tumours which are associated with later muscle invasiveness, and those with fairly benign behaviour.[19] In urological practice, however, patient management is still based on the aforementioned clinical (size, multicentricity) and histological (stage, grade) characteristics.[20] The only additional prognostic test which is being used by an increasing number of urologists is the histologic al examination of random urothelium biopsy specimens.

RANDOM UROTHELIUM BIOPSIES

During TUR, random urothelium biopsies can be taken from the cystoscopically normal-looking urothelium, and examined for the presence of dysplasia or carcinoma in situ. The presence of these dysplastic lesions is belie ved to reflect a premalignant state of the entire urothelial surface, from which multiple tumour formation is very likely. Recently, some evidence has been presented that this urothelial 'field defect' is not the result of the independent transformation of many urothelial cells, but that the progeny of a single transformed cell spread through the bladder, giving rise to topologically distinct but genetically related tumours.[16]

It is more than 30 years ago that the first report appeared on the potential prognostic value of concomitant microscopical lesions in macroscopically normal urothelium.[6] Since then, a number of studies have confirmed this prog nostic significance. However, these studies were very small and probably highly selective, whereas most of them did not assess the prognostic significan ce for the endpoint tumour progression. Furthermore, none of these studies evaluated prognostic significance, apart from the effect of the other available prognosticators. If the prognostic ability of intraurothelial dysplasia is caused by its association with, for instance, a low degree of differentiation of the primary tumour, then random biopsies may appear to be quite useless for patie nt management.

RATIONALE OF RANDOM BIOPSIES

In primary superficial bladder cancer, no definite consensus has been reached on treatment policy so far. The principal aim of taking random urothelium biopsies is to improve the urologist's ability to distinguish between patients who should be treated with adjuvant intravesical instillations and those who should not. Therefore, even if concomitant dysplastic lesions in random biopsy specimens prove to have prognostic ability, this does not necessarily justify taking biopsies from all newly diagnosed patients. Among other factors, it is also important to consider the number of patients who have dysplastic abnormalities in normal-looking mucosa, as well as the proportion of this grou p of patients who would have been treated with adjuvant instillations anyway. Thus, once the prognostic ability of random biopsies has been verified, a decis ion-analytical approach should be used to evaluate the rationale of the implementation of this test in everyday urological practice.

PREDICTION IN INDIVIDUALS

After the determination of a set of prognostic factors which are going to be used in clinical practice, it is important to evaluate the value of the complete set for patient management. In many situations, the value of prognosticators is claimed with statistical significance only. Statistical significance, however, does not in any way quantify the extent to which a test can differentiate between patients with a good prognosis and patients with a poor prognosis. Hazard ratios resulting from the proportional hazards model (which is becoming increasingly popular for prognostic assessment) do have such quantitative meaning. In the diagnostic process, the post-test probability of disease can be calculated from the pre-test probability and the test's likelihood ratio. Similarly, in prognostic assessment, the post-test risk of disease outcome can be calculated from the pre-test risk and the prognostic test's hazard ratio. This post-test risk can also be calculated using a combination of prognostic

tests. In this case, the combination of hazard ratios is called a prognostic index.

With this prognostic index, one can differentiate high-risk subgroups of patients from low-risk ones, at least to some degree. The ability to segregate these subgroups would enable us to frame appropriate, and perhaps very different, therapeutic management regimes for each subset. If the prognostic index is valid, then on average, the predictions of disease outcome for these subgroups will be correct. This validity, however, does not imply that the prediction will be accurate for an individual patient. The accuracy may be very poor despite the presence of highly statistically significant prognosticators. On an individual level, it is this precision or predictive power (in combination with treatment efficacy) that determines the extent of overtreat ment or undertreatment. Recently, a number of possible measures have been described for the predictive power of a set of prognostic factors.[10] Until now, the predictive power of the available prognostic factors in superficial bladder cancer (with or without random biopsies) has never been assessed.

AIMS OF THIS THESIS

On the basis of the brief outline on superficial bladder cancer given above, the aims of this thesis were:

- To study trends in bladder cancer occurrence and mortality in the Netherlands.
- To study the prognostic significance of concomitant intraurothelial dysplastic lesions (detected by means of random urothelium biopsies) for recurrent tumour formation and disease progression in primary superficial bladder cancer.
- To quantify the predictive power of the available set of prognostic factors in primary superficial bladder cancer.
- To evaluate the rationale of the implementation of random urothelium biopsies in the management of patients with primary superficial bladder canc er.

In an attempt to answer most of these clinical epidemiological research questions, data were used from a bladder cancer documentation project. These data were compiled by a large number of urologists, pathologists and radiotherapists from hospitals in the south-eastern part of the Netherlands. This documentation project (Chairman: Dr R.P. Heijbroek) was supported financially by the Comprehensive Cancer Centres IKO (Nijmegen), IKZ (Eindhoven) and IKA-ST (Enschede).

The datamanagement and the administrative coordination of the project was carried out by the Comprehensive Cancer Centre IKO.

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CHAPTER 2

BLADDER CANCER MORTALITY IN THE NETHERLANDS, 1955-88

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SUMMARY

In 1955, 234 men and 116 women died from bladder cancer in the Netherlands. In 1988 the numbers were 794 and 317 respectively. After adjusting for the ageing of the Dutch population since 1955, female mortality rates per 10^5 person-years appear to be very stable: 2.9 from 1955 to 1959 and 3.0 from 1985 to 1988. By contrast, an increasing trend exists in males. From 1955 to 1959 and from 1985 to 1988, bladder cancer mortality rates per 10^5 person-years were 7.5 and 12.4 respectively. For men in particular, increasing mortality (and incidence) rates are seen all over the world. In many cases this increasing trend is thought to originate from a higher risk of dying from bladder cancer in successive birth cohorts rather than from a higher risk in successive calendar periods. This so-called cohort effect is explained by changes in smoking behaviour in the male population.

Statistical modelling of bladder cancer mortality data from 1955 to 1988 in the Netherlands shows that the increasing temporal trend in men can also be described as a cohort effect. The risk of dying from bladder cancer increases from the 1875 birth cohort to the 1910 birth cohort, but decreases thereafter. It is concluded that this decreasing risk for generatio ns born after 1910 will probably result in a decreasing trend in mortality in the near future, when more and more of these "youngsters" reach the age of 70+.

INTRODUCTION

An increase in the incidence and mortality rates of bladder cancer is seen in nearly all Western communities.[24] In Alberta, Canada, male age-standardised incidence rates per 10^5 person-years increased from 10.8 in 1964 to 20.3 in 1984.[2] National cancer survey data from the USA showed a 51% increase in age-standardised rates among white men from 14.1 to 21.3 cases per 10^5 person-years in 1937 to 1939 and 1969 to 1971 respectively. In the same period the rates in Connecticut rose from 10.6 to 23.4.[18] In Denmark, the age-standardised incidence rates for men increased from 10.8 in 1953 to 1957 to 24.7 in 1978 to 1982.[10,19] Trends in bladder cancer incidence among women are less consistent. Although a number of registries showed increasing rates, in the US national cancer survey data for example, decreasing rates were found for women.

This presentation of rates from different calendar periods is more or less the standard method of describing temporal trends in the occurrence of cancer. It is possible, however, that period of birth, in stead of period of mortality, gives a better description of the observed rates. The relevance of differentiating these 2 types of temporal trend is that they may lead to very different hypothesised underlying causal factors.[8]

Using data from the Connecticut cancer registry Roush *et al.*[22] demonstrated that the increase in (invasive) bladder cancer rates could be accounted for by a simple so-called age-cohort pattern in both sexes. This means that starting with some specific birth cohort the incidence is increasing for successive birth coho rts (with a similar age profile) rather than for successive calendar periods. In the Connecticut analyses males show a consistent rise beginning at least with those born in 1870 and a peak in those born around 1930, whereas for females a sharp rise begins around 1900 with the increase persisting into at least the 1940 cohort. According to the authors these findings are consistent with trends by birth cohort for cigarette smoking, which strengthens the hypothesised association between cigarette smoking and bladder cancer.

In this report temporal trends in the occurrence of bladder cancer in the Netherlands are summarised. Since a national cancer registry from which incid ence data can be obtained has started only recently. Mortality statistics from the Dutch Central Bureau of Statistics from 1955-1988 are used for analyses. Statistical modelling is used to examine whether temporal variations in rates are attributable to a cohort effect and/or to a calendar period effect. The results from this modelling are also used to obtain some indication of a change in temporal trend in the near future.

METHODS

In the Netherlands, the Central Bureau of Statistics (CBS) has registered underlying causes of death since 1900. The number of men and women with bladder cancer as cause of death, as well as age and sex specific numbers of the Dutch population, were abstracted from the annual publications of the CBS for the years 1955 to 1988.[5] In this time period 4 revisions of the International Classification of Diseases were used. For the sixth and seventh revisions, ICD-code 181.0 and for the eighth and ninth revisions ICD-code 188 were used as definitions for bladder cancer. Only a small difference exists between the ninth revision and the former 3, using these codes: in the ninth revision the urachus is coded under "bladder cancer", whereas in the former editions the urachus is coded under "other urinary organs".

For statistical analysis the numbers of bladder cancer deaths were organised according to 5-year age groups and 5-year calendar periods of registration. Rates per 10^5 person-years based on these numbers are illustrated in Tables 2. 1 and 2.2. Ages under 35 were ignored because of the rarity of mortality from the disease under this age. The highest age-group (85+) was also ignored beca use no specific period of birth can be defined for this birth cohort. Birth cohorts were defined by combining age and calendar periods (see step lines in Tables 2.1 and 2.2).

To compare bladder cancer mortality rates in different calendar periods, adjustment for the change in age distribution of the Dutch population is necessary. Thus mortality rates in 7 successive calendar periods from 1955 to

1959 to 1985 to 1988 were age-standardised to the European standard population. This means that for each calendar period we calculated what the mortality rate in this standard population with a constant age distribution woul d have been if it had experienced the same age-specific mortality as the Dutch population.

TABLE 2.1 *Age-specific bladder cancer mortality rates per 100,000 man-years in the Netherlands, 1955-1988*[*]

Age	Calendar year of mortality						
	1955-1959	1960-1964	1965-1969	1970-1974	1975-1979	1980-1984	1985-1988
35-39	0 1	0 3	0 4	0 2	0 1	0 2	0 4
40-44	0 8	0 6	0 9	0 9	0 6	0 4	0 6
45-49	2 4	1 9	2 3	2 1	2 7	1 8	1 8
50-54	4 5	6 7	5 1	5 7	5 7	4 0	4 8
55-59	10 3	10 7	12 0	11 8	11 2	11 6	9 9
60-64	15 6	20 2	23 7	24 6	22 4	23 5	23 3
65-69	22 7	31 9	36 8	42 1	42 8	44 2	39 6
70-74	42 6	47 2	59 0	66 5	71 7	68 6	68 4
75-79	66 8	67 9	80 2	93 9	95 5	113 2	117 5
80-84	73 6	107 4	110 0	128 7	139 8	155 2	176 9

[*] *The step line indicates the 1910 birth cohort*

To estimate the separate effects of age, calendar period and birth cohort on trend in mortality, a simultaneous analysis of these factors was performed by use of a statistical model. A somewhat simple model is the multiplicative one, where the mortality for a specific age-period-cohort combination is, apart from random fluctuation, described as a product of these 3 factors.[11]

$$Y_{apc} = \alpha_a \pi_p \tau_c$$

where Y_{apc} is mortality rate for age group a, born in period c, as experienced during calendar period p; α_a is a factor describing the effect on mortality of age group a; π_p is a factor describing the effect on mortality of calendar period p; τ_c is a factor describing the effect on mortality of birth cohort c.

Such a model is also called a log-linear model, because by taking the logarithm (ln) on both sides of the equality sign one obtains a linear model:

$$\ln (Y_{apc}) = \ln \alpha_a + \ln \pi_p + \ln \tau_c$$

The age factor, period factor and cohort factor are fitted so that their products in all age period groups in Tables 2.1 and 2.2 are as close to the observed rates as possible. The statistical procedure used here for estimating the factors is the maximum likelihood method. The software package GLIM was used for computations.

To test the goodness-of-fit of the models with the observed mortality rates as well as to test the models against each other the Chi-square approximation to the -2 ln (likelihood-ratio) was used. For an explanation of log-linear models for analysis of temporal variation in cancer, 2 reports of Clayton and Schiffers are recommended.[6-7]

TABLE 2.2 *Age-specific bladder cancer mortality rates per 100,000 woman-years in the Netherlands, 1955-1988*[*]

Age	Calendar year of mortality						
	1955-1959	1960-1964	1965-1969	1970-1974	1975-1979	1980-1984	1985-1988
35-39	0.1	0.1	0.3	0.1	0.2	0.2	0.3
40-44	0.6	0.3	0.2	0.4	0.5	0.6	0.2
45-49	0.4	0.8	0.9	0.8	0.6	0.7	0.3
50-54	1.6	1.4	1.3	1.7	0.7	1.8	1.7
55-59	3.0	2.4	2.7	2.9	2.5	2.1	3.2
60-64	5.3	5.6	4.9	3.9	4.3	4.6	4.6
65-69	9.0	8.6	9.2	6.8	6.7	7.3	7.8
70-74	15.9	13.9	14.8	15.3	14.1	13.1	13.9
75-79	25.4	32.5	26.7	24.4	24.3	24.9	26.2
80-84	39.8	39.5	41.2	46.1	37.9	37.2	48.2

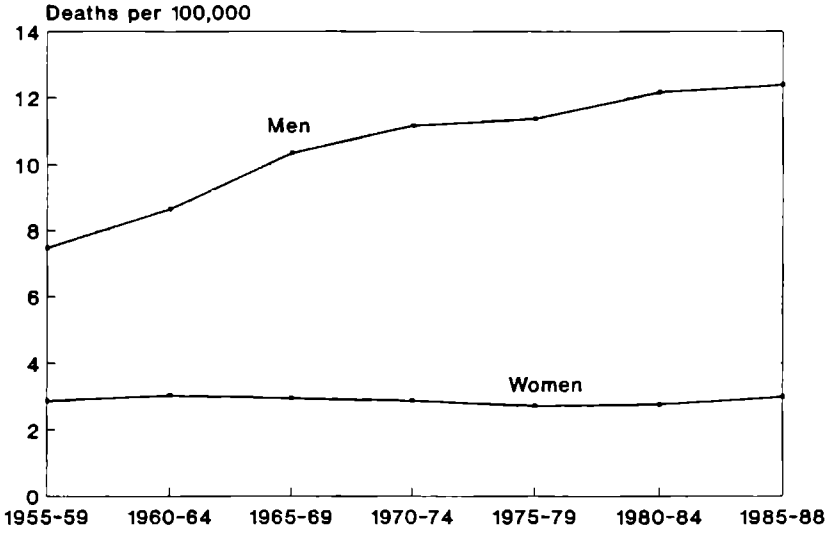
[*] *The step line indicates the 1910 birth cohort*

RESULTS

From 1955 to 1959 the age-standardised bladder cancer mortality rates per 10^5

person-years were 7.5 in men and 2.9 in women. From 1985 to 1988 therse rates were 12.4 and 3.0 respectively (Figure 2.1).

FIGURE 2.1 *Trend in bladder cancer mortality in the Netherlands between 1955 and 1988 (age-standardised to the European standard population)*



The increasing temporal trend in men seems to originate from a higher risk of dying from bladder cancer in the four oldest age groups (Figure 2.2). In men over 65 years of age the rates doubled in this 34-year time period. In women such an increase was not seen in the older age groups (Figure 2.3). Mortality rates were stable over time in all age groups, reflecting a situation of no temporal trend.

Since male mortality rates did not rise in all age groups, this suggests that a calendar period effect is not responsible for the increasing trend. Statistical modelling of the rates in men yields the results summarised in Table 2.3. Model 1 is the model which assumes that there is no temporal trend in male bladder cancer mortality. Since an increasing trend exists in male bladder cancer mortality, this model gives a very poor description of the data. This is reflected in the relatively large deviance from the model compared with the number of degrees of freedom (df). If a model gives a good description of the observed rates the deviance from the model is about the same as the number of df and far from significant. In that situation the *P* value is close to 0.50.

FIGURE 2.2 *Age-specific bladder cancer mortality in Dutch men according to registration period*

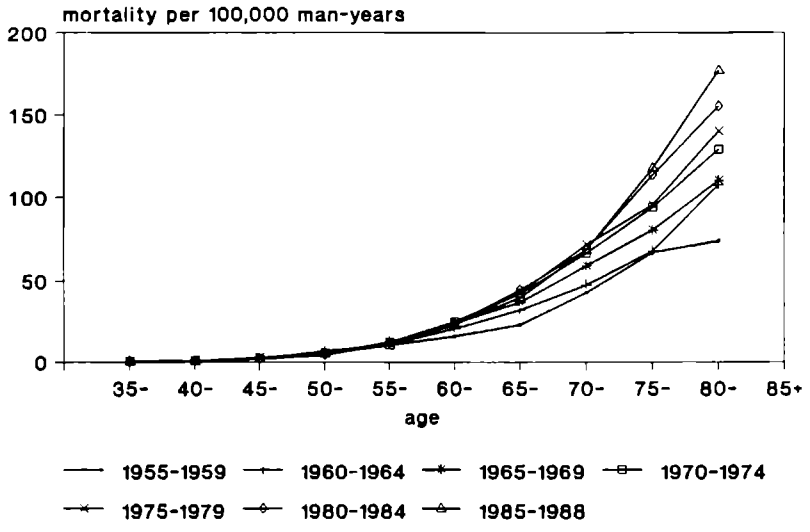
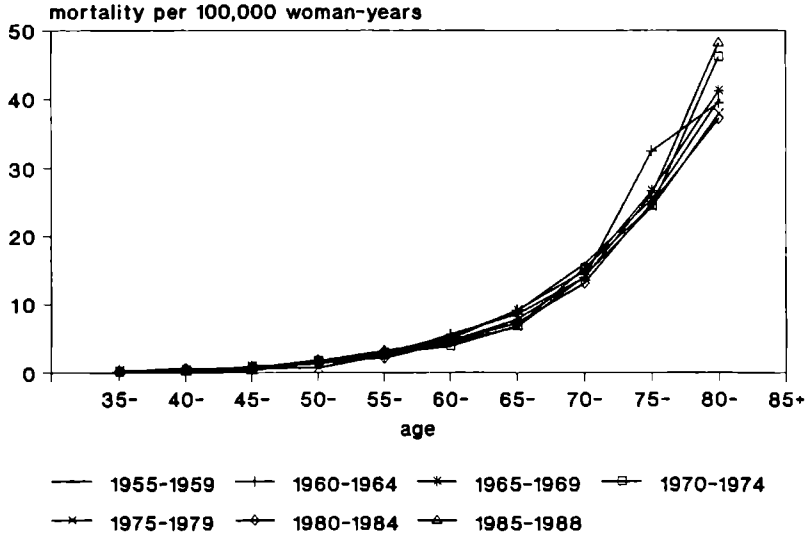


FIGURE 2.3 *Age-specific bladder cancer mortality in Dutch women according to registration period*



Since the P value in the age-only model is very small the model does not hold, which means that there is some temporal variation.

TABLE 2.3 *GLIM statistics for bladder cancer mortality in the Netherlands*

Males	Model		Deviance	df	P
	(1)	Age[@]	555.2	60	< 0.001
	(2)	Age + Drift[#]	234.6	59	< 0.001
	(3)	Age + Period	182.9	54	< 0.001
	(4)	Age + Cohort	53.3	45	0.19
	(5)	Age + Period + cohort	37.8	40	0.57
		Model (4) vs. Model (5)	15 5	5	0.01

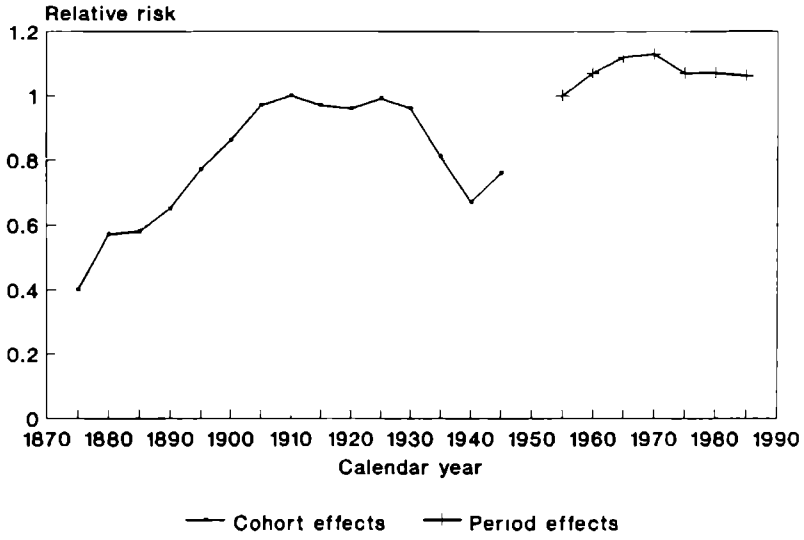
[@] *The AGE model describes the situation in which rates are predicted by age factors only and represents the null hypothesis of no temporal variation*

[#] *The AGE + DRIFT model is a model with temporal trend in which no distinction can be made between period effects (model 3) and cohort effects (model 4)*

The simplest model to describe temporal variation is the so-called age-drift model.[6] If this age-drift model gives a good description of the data, then a temporal trend exists for which no distinction can be made between period effects and cohort effects (model 2). However, the age-drift model does not hold either, since there is large deviance from the model. The next two models to consider are the age-period model (model 3) and the age-cohort model (model 4). Obviously the variation in bladder cancer mortality rates is much better explained by cohort effects than by calendar period effects. Unlike the age-period model, the age-cohort model provides an adequate description of the data (there is no significant deviance from the model: $P = 0.19$).

The parameter estimates τ_c from the age-cohort model are interpretable as relative risks between 2 birth cohorts. Defining the 1910 cohort as a reference group, the relative risks of bladder cancer mortality in Dutch men are illustrated in Figure 2.4. It can be seen that mortality increased until this 1910 cohort. Figure 2.4 also shows that the relative risk of dying from bladder cancer decreases for successive younger birth cohorts after the 1910 cohort. For example, compared with men born in 1910, the risk of dying from bladder cancer for men (of the same age) born in 1940 is only 67%. The standard graphical presentation of temporal trends (Figure 2.1) fails to identify this decreasing risk experienced by recent cohorts. Next to a cohort effect, a calendar period effect cannot be ruled out since there exists no significant deviance from the age-period-cohort model (model 5) as well ($P = 0.57$).

FIGURE 2.4 *Relative risk of male bladder cancer mortality in the Netherlands according to year of birth and registration period*



Compared with the age-cohort model this full age-period-cohort model gives a significantly better fit to the observed rates ($P = 0.01$). It is hard to assess, however, how great this calendar period effect is, because there is a major difficulty in the use of the age-period-cohort model. Knowing any 2 of age at death, year of birth and year of death fixes the third. Thus the 3 variables are not independant. A consequence of this relationship is that the solution from the model is not unique, although each solution produces the same fitted rates.[20] To overcome this problem one of all solutions from the age-period-cohort model was chosen in which the cohort effect is the same as in model 4: the age-cohort model. Through this, the period effect is identified. Taking the first calendar period (1955-1959) as reference, the relative risks of dying from bladder cancer in more recent calendar periods appear to be close to 1 (Figure 2.4). Although the inclusion of a period effect describes the observed rates significantly better than the age-cohort model, the period effect is not relevant quantitatively.

DISCUSSION

When the incidence rates of a particular cancer are changing with time, the first question to be asked is whether the change represents a real change in disease occurrence or simply a change in diagnostic / registration practice or acuity. In the case of trends in mortality rates also, a change in prognosis is

possible. Examples of changes in diagnostic / registration practice might be changes in (1) the definition of the malignancy, (2) histological confirmation, (3) autopsy rate and (4) diagnostic accuracy.[23] Differences or changes in applied therapeutics are another possible explanation of trends in mortality.

As stated before, there were no important changes in the definition of bladder cancer in the 4 revisions of the ICD used by the Dutch Central Bureau of Statistics. Furthermore, changes in histological confirmation and autopsy rate will presumably not be very important for bladder cancer. A change in histological confirmation is more relevant in the case of cancers that can be classified under 2 or more different rubrics, such as lymphomas of the gastrointestinal tract, or when specific histological subtypes of a tumour are studied. A change in histological confirmation is also important when cancer sites are studied to which other cancers frequently metastasise, *e.g.* lung and liver cancer. A change in autopsy rate is more relevant if tumours are studied that may remain latent, such as prostate cancer.

Changes in diagnostic and registration accuracy probably have less impact on bladder cancer mortality than on bladder cancer incidence. One of the most important registration problems in bladder cancer incidence is the classification of papillomas. Because of the absence of criteria which allow a clear distinction between papillomas with benign behaviour and those that will eventually manifest malignancy, for the last two decades non-invasive papillomas were notified to cancer registries more frequently. This change in policy may bias bladder cancer incidence rates but will have less effect on bladder cancer mortality.

In recent decades, survival rates of patients suffering from bladder cancer have shown a tendency to increase. In Alberta, Canada, the 5-year survival rate for men increased from 52% in 1964 to 65% in 1988.[2] However, if this increase is due to an increase in the proportion of superficial bladder cancers (pTa and pT1), the apparent improvement in treatment results may have little effect on mortality statistics.[24] It is not known whether this is the case in the Netherlands.

If one is satisfied that a change in incidence or mortality is not an artefact but real, it is interesting to identify the environmental or other changes that might be responsible. In identifying the factors responsible for the change in rates it is helpful to differentiate calendar period and birth cohort patterns in the data by means of statistical modelling.[8] A calendar period model suggests an immediate (or a fixed delayed) effect upon incidence (or mortality) which is constant across all age groups. A birth cohort model suggests an effect which affects rates in a specified generation equally throughout life.

Whereas no temporal trend was observed in female bladder cancer mortality in the Netherlands, for male bladder cancer mortality the increasing trend was found to be due mainly to a cohort effect. This difference between male and female trends in mortality is seen all over the world.[1,14,16,24,25] The fact that there is no temporal trend in mortality in women also lends support to the idea that the temporal trend in men is not caused by an artefact.

The cohort effect in men shows an increasing trend for successive birth cohorts until those born after 1910. The same was reported for England and Wales male mortality by Armstrong and Doll.[1] In Italian male mortality the increasing trend lasts at least until the 1935 cohort.[6]

Almost all authors correlate the cohort effect with the rise in cigarette consumption, the best known risk factor in bladder cancer. Differences in trends in males and females could also be attributed to smoking.[1,9,12,16-17,21,24,25] Other risk factors may also have an effect on bladder cancer occurrence. The most important of these potential risk factors is exposure to carcinogenic dye-stuffs, *e.g.* β-naphtylamine and benzidine, in certain occupations. However, although the relative risk of this factor is perhaps reasonably large (4.6 according to La Vecchia *et al.*),[15] the effect on trends in occurrence will probably be small because the proportion of the population that is exposed to these dyes is small.[17]

If cigarette consumption is indeed the aetiologic factor responsible for the increasing bladder cancer mortality and incidence rates, then presumably trends will decline in the near future, since more and more people will be life-long non-smokers. For example, in the Netherlands there has been a sharp fall in the proportion of smokers among men from 90% in 1958 to 44% in 1984. Such a decline is not yet visible in the more or less standard method of illustration of temporal trends (Figure 2.1). When this effect can be expected is hard to tell. Among other factors, this depends especially on the proportion of the disease attributable to smoking and the length of the latent period of bladder cancer. Considering the relative risks for successive male birth cohorts (Figure 2.4), perhaps the decline will be seen within the next decade when more cohorts with a decreasing relative risk will reach ages over 70. In this respect, it is also illustrative that the incidence of lung cancer and laryngeal cancer is already declining in Scotland,[3] since the length of the latent period for these smoking-related cancers is presumed to be shorter than that for bladder cancer.[13,17,24] Perhaps the relatively long latency for bladder cancer is also the reason why, contrary to lung cancer mortality in females, which has been rising steeply since 1980,[26] an increasing trend for bladder cancer mortality is not (yet) seen in Dutch women.

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CHAPTER 3

BLADDER CANCER INCIDENCE AND SURVIVAL IN THE SOUTH-EASTERN PART OF THE NETHERLANDS, 1975-1989

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SUMMARY

Trends in cancer occurrence and survival may reflect changing risks and prognosis, respectively, but may also be caused by changes in detection, classification and registration. Changed classification of low-stage papillary carcinomas may have a material effect on observed trends in the occurrence of bladder cancer. We studied the effect of the implementation of the WHO 'grading system' and the third edition of the TNM staging system on bladder cancer incidence in the south-eastern part of the Netherlands.

Data on superficial and invasive bladder cancer incidence between 1975 and 1989 were derived from the population-based Eindhoven cancer registry. Data on survival of patients with stages I-IV bladder cancer were derived from the municipal population registers.

Bladder cancer incidence per 100,000 person-years (age-adjusted to the European standard population) rose from 25.9 to 40.7 in males and from 3.1 to 8.5 in females. This increasing trend was caused almost entirely by non-invasive pTa papillary carcinoma. In 1975, not one pTa tumour was recorded by the cancer registry, whereas in 1989 the incidence rates were 15.7 and 3.6 in males and females, respectively. A considerable shift was observed towards lower disease stages, which was less evident within the group of invasive tumours. The relative 5-year survival of patients with stages I-IV invasive bladder cancer was 59% in 1975 to 1977 and 70% in 1984 to 1986. After stratification by stage, however, no striking improvement was observed in the prognosis.

We conclude that the increasing trend of bladder cancer occurrence in the Netherlands since 1975 has largely been caused by changed classification systems and reporting procedures for pTa tumours (formerly classified as 'papillomas'). However, there may have been a small increase in the risk of invasive bladder cancer in females.

INTRODUCTION

One of the major problems in cancer registration is the reporting and classification of low-grade noninvasive papillary shaped bladder tumours.[1] This problem relates particularly to the distinction between papillary shaped tumours with benign behaviour and those that will eventually manifest (progressive) malignancy if left untreated. As such non-invasive carcinomas can form a substantial proportion of all bladder tumours and treatment may prevent them from progressing to invasive disease then the incidence of malignant bladder cancer probably relates to differences in urological care.[2]

Furthermore, changes in the reporting and classification of these low-stage papillary tumours have resulted in biased trends in time of both bladder cancer incidence and survival.[3] For the past 10 to 20 years, the pendulum of opinion

has swung firmly in favour of considering the great majority of these lesions malignant, albeit of low grade, and most pathologists presently diagnose almost all of these lesions that appear cytologically innocuous as noninvasive papillary urothelial carcinoma or transitional cell carcinoma grade 1.[4]

In this study we explored trends in incidence of bladder cancer from 1975 to 1989 in the south-eastern part of the Netherlands. Special emphasis is laid on changes in stage distribution and survival.

METHODS

Data source

Data on bladder cancer incidence and survival were derived from the population-based cancer registry in the area of Eindhoven.[5] The registry covers the south-eastern part of the province of North-Brabant and the northern part of the province of Limburg. It is considered to be complete in a core area with a population of approximately 850,000 since the early 1970s. Newly diagnosed cancer patients are notified to the registry through three pathology laboratories in the cities of Venlo, Helmond and Eindhoven and the Radiotherapy Department in the city of Eindhoven. Furthermore, the registry receives hospital discharge diagnoses from all the community hospitals in the area. After notification, professional registrars collect data from the clinical records.

We included all new patients with bladder cancer (International Classification of Diseases for Oncology: code 188)[6] diagnosed between January 1 1975 and January 1 1990. Diagnoses which were originally classified according to ICD revisions 8 and 9, were converted into ICD-O codes. There is no routine reporting of benign and/or unspecified papilloma of the bladder (ICD-O behaviour codes 0 and 1, respectively) in the cancer registry, so these tumours were not included. All the tumours were staged according to the TNM classification of malignant tumours.[7] See Table 3.1. The second edition of the TNM staging system was used until 1980, the third since that year. All new tumour occurrences in bladder cancer patients, whether or not in a higher tumour stage category, were considered to be recurrences.

Analyses

Incidence rates per 100,000 person-years in males and females were calculated for 1975 to 1989 inclusive. To adjust for the pronounced ageing of the population during this period, the incidence rates were age-adjusted to the European standard population.[8]

Trends in incidence rates were presented as 3-year moving averages (2-year averages were used for the first and last year of the study interval). The incidence rates were calculated separately for superficial and invasive tumours.

TABLE 3.1 *TNM stage grouping of urinary bladder cancer (UICC, 1987)*

Stage	Primary tumour	Regional lymph nodes	Distant metastases
0	Tis	N0	M0
	Ta	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3a	N0	M0
	T3b	N0	M0
IV	T4	N0	M0
	Any T	N1, N2, N3	M0
	Any T	Any N	M1

Superficial tumours comprise three stages of disease[7]: pTis, a flat non-papillary high-grade carcinoma of the mucosa; pTa, a papillary carcinoma confined to the mucosa; and pT1, a tumour which invades the lamina propria but does not involve the superficial muscle layer of the bladder wall (stage 0-I in the stage grouping; see Table 3.1).[@] The stage distribution as well as the mean age at diagnosis of bladder cancer was compared in five triennial calendar periods (1975-77; 1978-80; 1981-83; 1984-86; 1987-89).

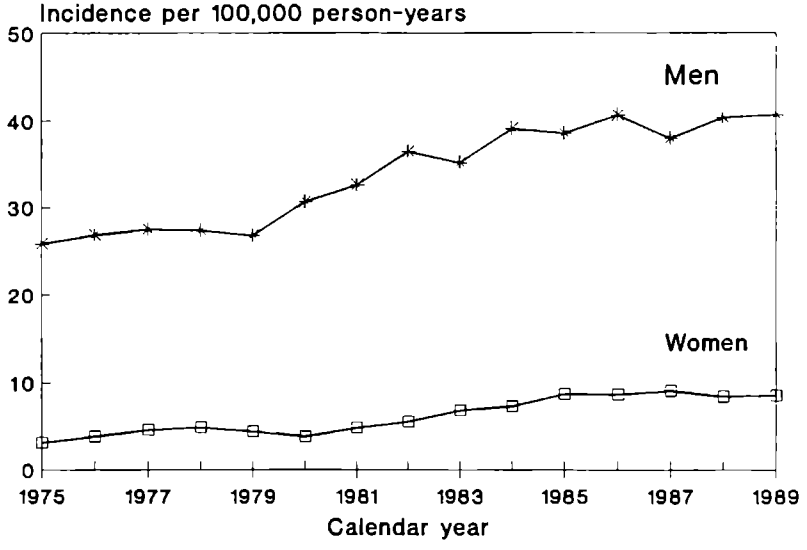
Except for patients with stage 0 disease (Table 3.1), data on vital status until July 1 1991 were collected from the municipal population registers. Less than 1% of all the patients were lost to follow-up. We calculated the actuarial relative survival rate as a measure of patient survival adjusted for the effect of mortality attributable to competing risks of death.[9] Relative survival was defined as the ratio between the observed survival rate and the survival rate which can be expected in a group of the general population similar to the group of patients at the time of diagnosis, with respect to age, sex and calendar time. We calculated the 5-year relative survival for patients diagnosed in the total study period, as well as for the successive calendar periods 1975-77, 1978-80, 1981-83 and 1984-86. The standard errors of the relative survival estimates were obtained using Greenwood's formula.[10] Owing to the relatively small number of female patients, the relative survival in successive triennial periods was calculated for both sexes combined. For the calculations, we used a computer programme developed by the Finnish Cancer Registry.[11]

[@] *Stage I (pT1 N0 M0) bladder cancer is defined as superficial in urology even though it is an invasive tumour according to the TNM classification*

RESULTS

Between 1975 and 1989, 1909 newly diagnosed patients with bladder cancer were registered, 1537 (80.5%) males and 372 (19.5%) females. Of all the tumours, 97.5% had been histologically verified (of which 0.2% at autopsy); 1.6% had been verified with urine cytology only, and in 0.9% no microscopical verification had taken place. 95.4% of the tumours were classified as transitional cell carcinoma (pure or mixed with another morphology), 2.2% as squamous cell carcinoma, 1.2% as adenocarcinoma and 1.2% had another or unknown morphology (including the cases without microscopical verification). These latter 1.2% (N=23) were excluded from further analyses.

FIGURE 3.1 *Bladder cancer incidence per 100,000 person-years in males and females in the south-eastern part of the Netherlands between 1975 and 1989. Rates are presented as 3-year moving averages after age adjustment to the European standard population*

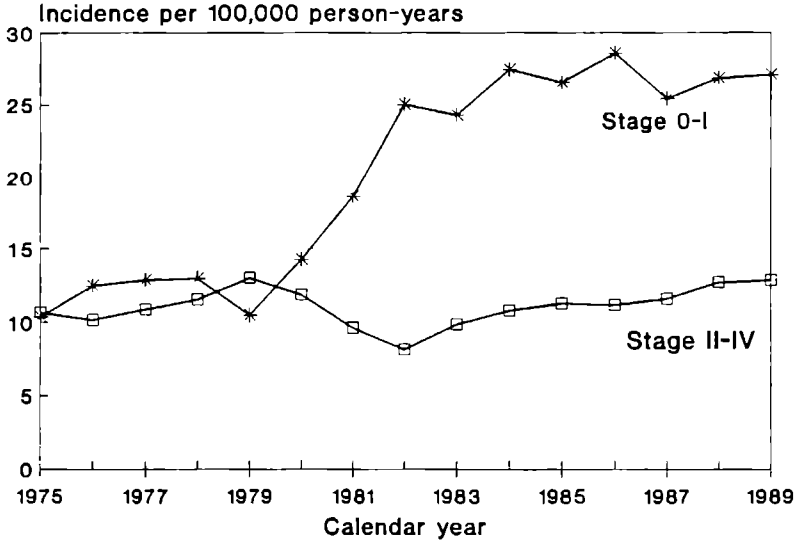


Incidence

Age-adjusted urinary bladder cancer incidence in men rose from 25.9 per 100,000 person-years in 1975 to 40.7 per 100,000 person-years in 1989. In women, these rates were 3.1 and 8.5, respectively. See Figure 3.1. This increase in bladder cancer incidence can be attributed almost entirely to an

increase in the number of superficial tumours reported (Figure 3.2). For men, the incidence of superficial (stages 0 and I) bladder cancer doubled in the first half of the 1980s. Except for a temporary decrease in the same period, the incidence of invasive bladder cancer (stages II-IV) increased only marginally from 10.6 per 100,000 person-years in 1975 to 12.8 per 100,000 person-years in 1989. An increase in the incidence of superficial bladder cancer was also seen in women (Figure 3.3). However, in women there seems to have been a small increasing trend in invasive bladder cancer as well (from 2 to 3 cases per 100,000 person-years).

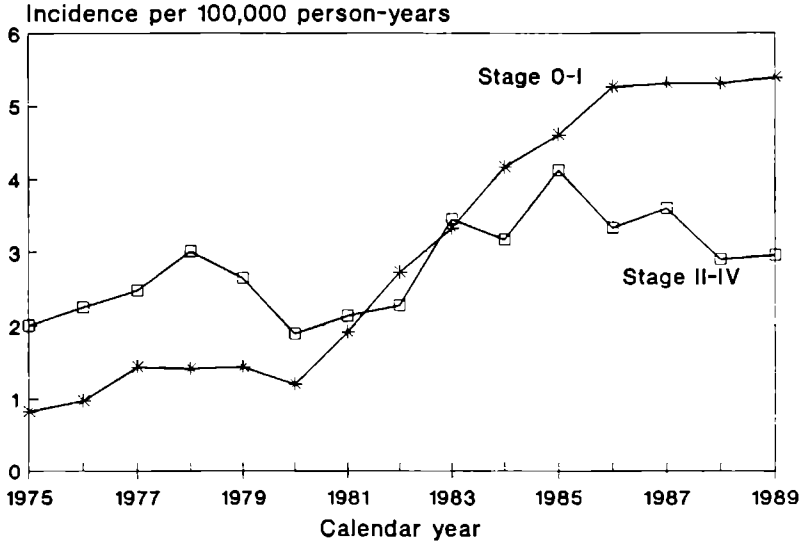
FIGURE 3.2 *Superficial and invasive bladder cancer incidence per 100,000 person-years in males in the south-eastern part of the Netherlands between 1975 and 1989. Rates are presented as 3-year moving averages after age adjustment to the European standard population*



Stage distribution

The increase in superficial bladder cancer (pTis, pTa and pT1) was caused almost entirely by an increase in noninvasive papillary pTa tumours. In 1975, not one pTa tumour was entered into the cancer registry. In 1989, the age-adjusted incidence of pTa tumours in males and females was 15.7 and 3.6, respectively. Flat intraurothelial pTis tumours and papillary or solid pT1

FIGURE 3.3 *Superficial and invasive bladder cancer incidence per 100,000 person-years in females in the south-eastern part of the Netherlands between 1975 and 1989. Rates are presented as 3-year moving averages after age adjustment to the European standard population*



tumours with invasion into the lamina propria of the bladder wall, hardly increased: the incidence of pTis and pT1 tumours was 10.4 in 1975 for males; the incidence in 1989 was 11.3. For females these rates were 0.8 and 1.8, respectively.

There has been a clear shift towards superficial tumours in the stage distribution of all bladder cancer (Figure 3.4). A shift towards lower disease stages was less evident when stage 0 tumours (pTis and pTa) were excluded (Figure 3.5), although it appeared that after 1980, relatively fewer tumours were diagnosed in stages III and IV.

The mean age at diagnosis remained almost constant during the study interval, despite considerable ageing of the population. In 1975-77 the mean age of newly diagnosed male bladder cancer patients was 67.4 years (SD = 11.2) and 6.2% of all the patients were diagnosed under the age of 50 years. In 1987-89, the mean age in males was 67.9 years (SD = 11.0), 6.3% of all the patients were younger than 50 years. The mean ages in women in the first and last triennial periods were 70.9 and 69.2 years, respectively. The proportion of female patients who were younger than 50 years at the time of diagnosis in the first and last triennial periods was 6.1% and 8.3%, respectively.

FIGURE 3.4 *Stage distribution of (male plus female) bladder cancer in the south-eastern part of the Netherlands in five successive triennial calendar periods*

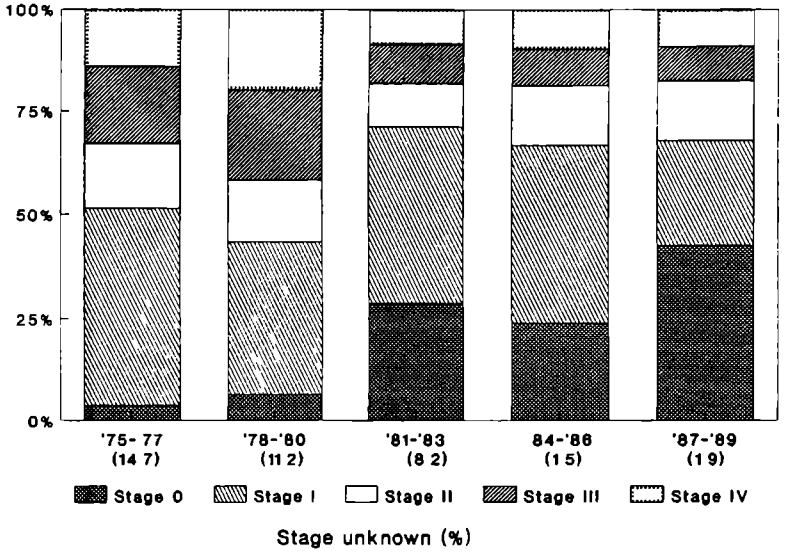
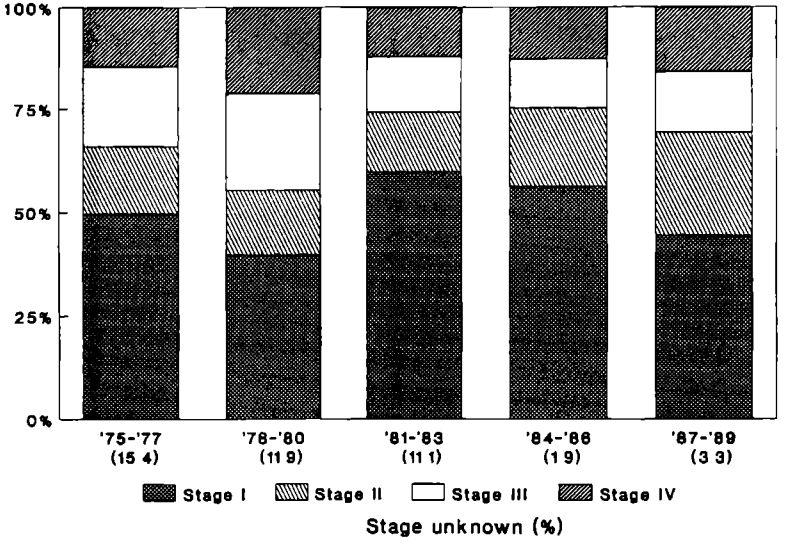


FIGURE 3.5 *Stage distribution of (male plus female) invasive bladder cancer in the south-eastern part of the Netherlands in five successive triennial calendar periods*



Relative survival

The observed cumulative five-year survival in male and female patients with stages I-IV bladder cancer in the total study period was 48%. The relative five-year survival was calculated to be 64% (95% CI: 60%-68%). On average, the male patients were diagnosed with lower staged disease than the female patients: 28% of the male patients with invasive disease had stage III or IV disease at diagnosis compared to 43% of the female patients. This favourable disease stage distribution resulted in a higher five-year relative survival for male patients: 69% (95% CI: 65%-73%) vs. 47% (95% CI: 38%-56%) in female patients. The relative survival of the patients diagnosed in the four successive triennial periods (for both sexes combined) is illustrated in Table 3.2. In the calendar period 1975-77, the relative survival was 59% (95% CI: 49%-69%). For the patients diagnosed between 1984 and 1986, the relative survival was 70% (95% CI: 63%-77%). The increase in relative survival was less evident after stratification by stage group. In the patients with stage I bladder cancer, the survival was 83% in 1975 to 1977 and 90% in 1984 to 1986. In patients with stages II-IV bladder cancer, the survival was 34% in the first and 41% in the latter triennial period. The confidence intervals show considerable overlap because of relatively small numbers.

TABLE 3.2 *5-year relative survival (S_5) of patients with invasive bladder cancer (95% CI)*

Calender period	Stage I			Stage II-IV			Stage I-IV		
	N	S_5	95% CI	N	S_5	95% CI	N	S_5	95% CI
1975-1977	92	83%	(70-96)	93	34%	(22-46)	185	59%	(49-69)
1978-1980	88	93%	(81-99)	134	45%	(34-56)	222	65%	(56-74)
1981-1983	151	83%	(73-93)	103	35%	(23-47)	254	64%	(56-72)
1984-1986	201	90%	(82-98)	155	41%	(31-51)	356	70%	(63-77)

DISCUSSION

Between 1975 and 1989, bladder cancer incidence in the south-eastern part of the Netherlands almost doubled in males and more than doubled in females. In both sexes, this increasing trend appeared to be caused almost entirely by an increase in the number of diagnoses of noninvasive papillocarcinoma (pTa) entered into the cancer registry, which resulted in a shift towards a more favourable disease stage distribution (Figure 3.4). Within the group of invasive bladder cancer (stages I-IV) the shift was not so evident (Figure 3.5).

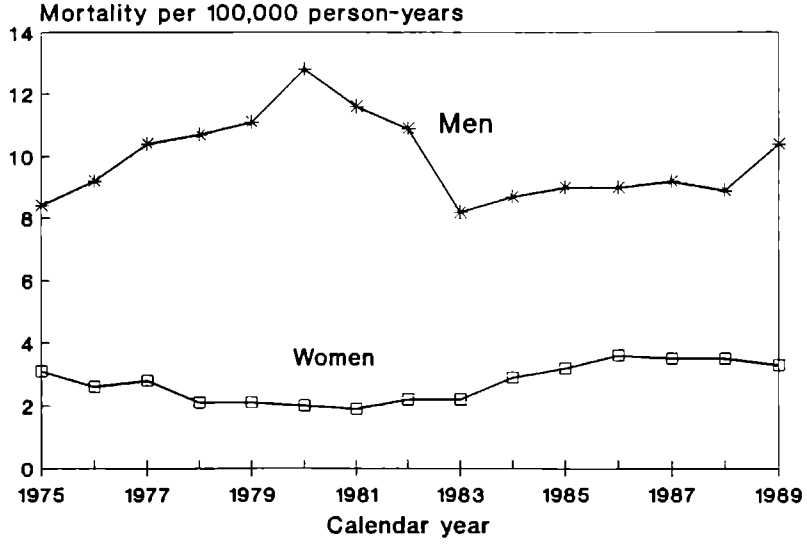
These findings raise serious doubts as to whether or not the increasing trend in bladder cancer occurrence reflects a real increasing risk. It is more likely that there has been a change in classification and/or registration practice. Until the WHO grading system was implemented in 1973[12] all low-grade non-invasive papillary shaped tumours were called 'papillomas'. After 1973, pathologists and urologists started to define tumours with 'the least degree of cellular anaplasia compatible with a diagnosis of malignancy' as grade 1 papillocarcinomas.[13] It took a number of years, however, before these tumours were reported to and/or entered into the cancer registry. Until the third edition of the UICC TNM classification became available (in 1978), which the Eindhoven registry started to use in 1980, there was no separate code for noninvasive papillocarcinoma. Classifying these tumours as pTis would have been wrong because flat carcinoma in situ of the bladder is known to be a relatively aggressive lesion which is often widespread over the urothelium and (by definition) poorly differentiated. It was only after the implementation of the 3rd edition of the staging system that all papillary noninvasive tumours with some degree of morphological atypia were classified as papillocarcinomas (pTa).

In theory, the increased incidence of pTa tumours could have also resulted from earlier diagnosis due to improved acuity and heightened public awareness. However, a substantial reduction in diagnostic delay is unlikely in the Netherlands where all the inhabitants have easy access to medical care and there are no long urological waiting lists (not even in 1975 when the number of urologists in the Eindhoven region was only 7 compared to 14 in 1989). The initial symptom in more than 80% of the male and more than 70% of the female patients with bladder cancer is macroscopical, painless haematuria.[14-15] This symptom will probably be enough reason to seek medical care. It is possible that there may occasionally be some delay in the diagnosis of bladder cancer, caused by the patient himself or by the general practitioner. Such a delay could exist, for example, in patients with cystitis as the presenting symptom instead of haematuria and in female patients in whom haematuria may be attributed to infection.[14] Although this may be an explanation for the differences in disease stage distribution and survival between males and females, there is little reason to assume that this diagnostic delay has changed over the years. In recent years, more low-stage bladder tumours may have been diagnosed as a coincidental finding during transurethral resection of the prostate or with a routine medical examination (microscopical haematuria). However, this cannot explain the pronounced increase in pTa bladder cancer in the first half of the 1980s. The same holds true for new techniques, such as flow cytometry using monoclonal antibodies. A careful history, physical examination, cytology and cystoscopy are still the accepted diagnostic methods.[16] New diagnostic approaches will probably be implemented in the follow-up of cancer (prognostic tests) rather than at initial diagnosis.

As mentioned above, an alternative explanation for the increased incidence of pTa bladder cancer, is a real increase in the risk of developing this disease.

The major risk factor for bladder cancer in males and females is smoking.[17] It has been suggested that smoking as an aetiological factor is largely confined to noninvasive bladder cancer.[18] However, in a recent study in Denmark, the influence of smoking on bladder cancer risk appeared to be similar for low and high stage tumours as well as for low and high grade tumours at diagnosis.[19] The prevalence of smoking among male adults in the Netherlands decreased from 90% in the 1950s to about 40% in the 1980s, whereas women exhibited an increase from 20% to 40%. These changes in smoking behaviour have led to a decrease in lung cancer incidence and mortality since 1980 in men, and an increase in women since 1975.[20] Although we have not yet observed any similar trends for bladder cancer mortality in the Eindhoven region (Figure 3.6), it has already been shown that the risk of dying from bladder cancer in the Netherlands decreases in successive male birth cohorts.[21]

FIGURE 3.6 *Bladder cancer mortality per 100,000 person-years in males and females in the south-eastern part of the Netherlands between 1975 and 1989. Rates are presented as 3-year moving averages after age adjustment to the European standard population (Source: Central Bureau of Statistics, the Netherlands)*



Therefore, one would expect a decreasing trend in male bladder cancer incidence, if any, rather than an increasing one (Figure 3.1). In women, a slight increase in bladder cancer was expected but one would not expect it to

be confined to superficial tumours almost entirely (Figure 3.3). Thus, apart from a small increased risk of invasive bladder cancer in females, it is highly likely that the increase in urinary bladder cancer incidence is the result of changing classification following the implementation of the WHO grading system and the third edition of the TNM staging system.

The actuarial relative 5-year survival in male and female patients with invasive bladder cancer was 70% in 1984 to 1986 compared to 59% in 1975 to 1977. One has to bear in mind, however, that the relative survival only compares the observed survival to the expected survival in a given population. It does not adjust for differences in the distribution of tumour and host characteristics in patient populations diagnosed in successive calendar periods. Therefore, we also calculated the relative survival after stratification by stage (Table 3.2). It appeared that the trend towards a higher survival in more recent years had almost disappeared, although small numbers complicated the interpretation of the results.

The absence of any real trend in stage-specific survival rates since 1975 is not very surprising. Over the past 15 years, there have been no major changes in the treatment of stages II-IV invasive bladder cancer. As in the late seventies, the treatment of invasive bladder cancer comprises either radiotherapy alone, radical cystectomy alone, or occasionally a combination of these modalities. The radiotherapy techniques (with simulation and linear accelerators) and cystectomy techniques (with the development of continent forms of urinary diversion and nerve-sparing approaches) have been improved but have not led to a significantly better prognosis.[22] Recently, some promising results from neoadjuvant chemotherapy regimens (such as M-VAC) have been reported,[23] but the ultimate benefit of these regimens remains yet to be proven.[24]

In contrast with stages II-IV bladder cancer, progress has been achieved in the management of stages 0-I bladder cancer. The past two decades of clinical experimentation have provided convincing evidence that adjuvant intravesical chemotherapy, after transurethral tumour resection, lowers the recurrence rate.[25] Furthermore, the intravesical administration of Bacillus Calmette-Guérin (BCG) causes a significant reduction in the rate of relapse and prolongs the relapse-free interval.[26] However, the ability of cytotoxic drugs and BCG to prevent progression to muscle invasion, metastatic bladder cancer and death from bladder cancer, is still a matter of debate.[27] Thus, although innovations in treatment management may have improved the quality of life of patients with invasive bladder cancer, as well as the recurrence-free interval of superficial bladder cancer, they may have less merit with regard to the ultimate disease outcome.

We conclude that over the past 15 years, there has been no clear shift towards a more favourable disease stage distribution or a far better prognosis in patients with primary invasive bladder cancer. There has been a small increase in the occurrence of invasive bladder cancer in females. The increase

in the occurrence of superficial bladder cancer which has caused a relative shift towards lower disease stages, can be explained by changes in classification and is therefore artificial

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CHAPTER 4

THE CLINICAL EPIDEMIOLOGY OF SUPERFICIAL BLADDER CANCER

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SUMMARY

Even though the majority of patients with bladder malignancies initially present with low stage disease, the clinical epidemiology of these so-called superficial bladder tumours is not well known. In this paper, disease characteristics at initial presentation and during follow-up are described in 1745 primary cases documented prospectively in the Netherlands. The risk of recurrent disease after primary treatment is very high: in 60% of cases, at least one recurrence is diagnosed within 5 years (95% CI: 58%-62%). In patients with a small solitary pTa grade 1 tumour, the 3-year recurrence risk is 37%. In patients with multiple large high grade pT1 tumours, this risk is as high as 77%, despite a significant beneficial effect of adjuvant intravesical chemotherapy. The actuarial risk of disease progression is 10.2% after 3 years (95% CI: 8.6%-11.8%). This risk of progression depends on the patient's age at diagnosis, tumour stage, grade and multiplicity. The use of intravesical instillations with chemotherapy or BCG vaccine after TUR does not prevent progressive disease, although this finding is difficult to interpret from a non-randomised study. The five-year relative survival in patients with superficial TCC of the bladder is 86% (95% CI: 84%-88%).

INTRODUCTION

Bladder cancer is a heterogeneous disease with an unpredictable clinical course. In urology practice, bladder cancer cases are differentiated on the basis of the extent of bladder wall invasion. The largest group is the group of superficial transitional cell carcinomas (TCC). Patients with superficial TCC have a fairly good prognosis with a 5-year relative survival of 80% to 90%.[4] Therefore, the greatest concern in these patients is not to reduce mortality but to lower and postpone the number of recurrences (which are very common in superficial TCC) and thereby to prevent progression to invasive disease.[13] To accomplish this, initial treatment by transurethral resection (TUR) is often followed by intravesical instillations with chemotherapy or immunotherapy.

Until now, all knowledge of disease characteristics of superficial bladder cancer (such as stage distribution, the risk of recurrences and disease progression and survival) has been based on fairly small case series which were often selective in one or more respects. In this paper, quantitative data of clinical epidemiological features of superficial bladder cancer are presented from a large case series in the Netherlands.

PATIENTS AND METHODS

In the southeastern part of the Netherlands, there has been a close cooperation

between urologists, pathologists and radiotherapists from 23 district hospitals, 1 university hospital and 6 radiotherapy centres since 1981 (the Dutch South-East Cooperative Urological Group). In 1983, this resulted in a consensus report on the diagnosis and treatment of patients with bladder cancer. Furthermore, it was agreed that the participating urologists would document every newly diagnosed bladder cancer patient. This documentation project started in 1983. Intake registration continued until January 1990. Follow-up registration continued until July 1991.

The following items of each patient with a primary bladder tumour were registered: date of birth, sex, date of histological confirmation, main complaint, tumour morphology, grade of differentiation (according to the WHO grading system)[20], localisation, TNM classification,[29] tumour multiplicity and intravenous urogram result. Furthermore, all participating urologists were asked to take (and document) at least four random quadrant biopsies in macroscopically normal-looking urothelium (left and right lateral wall, trigone and dome) at the time of resection of the tumour(s). The therapy to be applied was transurethral resection of the tumour (TUR) in all patients. Urologists were advised to consider adjuvant intravesical instillations with chemotherapy or BCG vaccine in the case of multiple tumours. In pT1 grade 3 patients more aggressive therapy, such as radical surgery or external or interstitial radiotherapy, would have to be considered. To detect recurrences, cystoscopy and urine cytology were used every three months in the first year after treatment. From the second year onwards, this check-up was performed every six months. Follow-up data concerning disease and life status were collected for each patient once every year.

Between 1983 and 1990, 2805 cases were documented. In 1991, all the data in the documentation project were reviewed using the medical files. After this check, the records of 100 cases were excluded. Of these, 30 had an inverted papilloma (which was considered to be benign), 58 had recurrent instead of primary disease at first registration, 5 did not have TCC in the bladder but in the upper urinary tract. In the records of 7 cases, there were major inconsistencies, which could not be corrected with information from the medical files. Of the remaining 2705 cases, 1745 (64.5%) had superficial TCC. "Superficial" is defined as tumour extension limited to the mucosa (pTa) or the lamina propria (pT1) of the bladder wall with or without carcinoma in situ in random biopsies. In urology practice, primary carcinoma in situ (pTis) is considered to be very different from pTa and pT1 tumours because of its relatively aggressive clinical behaviour. For that reason, patients with primary pTis (N=52 in our series) were not evaluated in this study.

Survival free of recurrence, survival free of progression and survival itself were measured from the date of histological diagnosis to the date of first recurrence, first evidence of disease progression and the date of death, respectively. Survival curves were based on the life table method, statistical significance being determined by the log rank test. The independence of host and tumour characteristics in determining survival free of recurrence and

progression was evaluated multivariately using the Cox proportional hazards model.[5]

Although the case series in this documentation project is large, registration was not population based, which implies that incidence rates cannot be calculated from the project. However, nine Comprehensive Cancer Centres in the Netherlands keep population based regional cancer registries. One of these registries (IKL), covering a population of approximately 850,000 in the southern part of the Netherlands, has complete data on the incidence of superficial bladder cancer since 1986.[26] Information from this registry from the period 1986-1989 was used to calculate age and sex-specific incidence rates. The population based cancer registry was also used to check whether patient intake in the documentation project was selective in any way. There appeared to be hardly any difference in age, sex, stage and grade distribution between the cancer registry and our case series, indicating no under or over representation in our series.

RESULTS

Incidence

In the southern part of the Netherlands, the total bladder cancer incidence rate per 10^5 person-years (age-standardised to the European standard population) is 36.3 for males and 6.7 for females. Superficial bladder cancer incidence rates for males and females are 23.7 and 3.9, respectively. This accounts for 65% of the total bladder cancer incidence in males and 58% in females. The proportion of all bladder cancers diagnosed as superficial disease is higher in the younger age categories than in the older ones (Figure 4.1). In males, the lifetime risk of developing bladder cancer (before the age of 75 years) is 2.8%. The risk of superficial bladder cancer is 1.9%. In females, these risks are 0.5% and 0.4%, respectively.

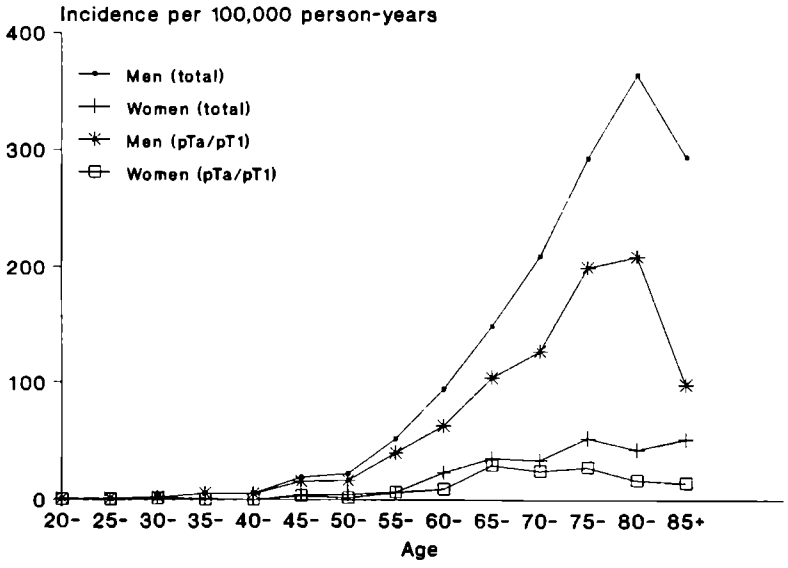
Initial presentation

In the documentation project, 1745 patients with superficial (pTa or pT1) TCC were registered. Characteristics of this group of patients at inital presentation are listed in Table 4.1: 32% of all the patients had a pT1 tumour; 16% of the tumours were classified with differentiation grade 3 and 29% had multiple tumours. Random biopsies of macroscopically normal-looking urothelium were taken in 1044 patients. In 22% of these patients, dysplasia or carcinoma in situ was diagnosed in at least one biopsy specimen.

The median age at the time of diagnosis was 67 years. There was a clear shift towards a higher disease stage with increasing age (Figure 4.2). In patients under the age of 40 years, pTa grade 1 or 2 disease accounted for more than 85% compared to only 52% in patients over 80 years of age. The proportion of patients diagnosed with multiple tumours was also different for these age groups: 13% versus 37%.

From the total group of patients, 64% were treated with transurethral resection only; additional intravesical instillations were administered in 32% of the cases and more extensive therapy was given in 4% of the cases (radiotherapy and/or cystectomy). The latter 4% were excluded from the analyses of the risks of recurrence and progression.

FIGURE 4.1 *Age-specific incidence rates of total bladder cancer and superficial bladder cancer in males and females in the province of Limburg (NL), 1986-1989*



Source: Comprehensive Cancer Centre IKL, Maastricht

First recurrence

The life-table (or actuarial) risk of recurrent disease after primary treatment in superficial bladder cancer was very high. Within 5 years, nearly 60% of all the cases had at least one recurrence (Figure 4.3). A proportion of this group of patients with a recurrence were prone to having more recurrences. The risk of recurrent disease in the first year of follow-up was 33% (95% CI: 31%-35%). In the second year of follow-up, this risk was as high as 47% among the patients who had already had recurrent disease, compared to only 18% of the patients without recurrence in the first year of follow-up.

The risk of recurrent disease in superficial bladder cancer was dependent on a number of prognostic indicators. In the univariate analyses, tumour stage (pT1 vs. pTa), degree of differentiation (grade 3 vs. 2 vs. 1), multiplicity

TABLE 4 1 *Clinical characteristics at disease presentation and the therapy applied in 1745 patients with primary superfical TCC*

	N	%
Sex		
Men	1415	81 1
Women	330	18 9
Age		
≤ 39	46	2 6
40-49	103	5 9
50-59	295	16 9
60-69	550	31 5
70-79	546	31 3
80+	205	11 7
Main complaint (N=1227)		
Haematuria	991	80 8
Irritative bladder symptoms	156	12 7
Not urological	80	6 5
Stage		
pTa	1187	68 0
pT1	558	32 0
Grade[a]		
1	669	38 4
2	793	45 4
3	283	16 2
Multiplicity		
Solitary	1223	70 1
Multiple	510	29 2
Unknown	12	0 7
Areas involved		
Neck only	27	1 5
Trigone only	55	3 2
Posterior wall only	123	7 0
Right lateral wall only	384	22 0
Left lateral wall only	390	22 3
Dome only	38	2 2
Anterior wall only	25	1 4
2 Areas	373	21 4
3 Areas	166	9 5
≥ 4 Areas	164	9 4
Quadrant biopsies (N=1044)		
No abnormalities	816	78 2
Dysplasia in 1 or more areas	142	13 6
Carcinoma in situ	86	8 2
Therapy		
TUR only	1116	64 0
TUR + instillations	558	32 0
TUR + (Partial) cystectomy or interstitial radiotherapy	71	4 1

[a] *In cases with different grades in one tumour, the highest grade was documented*

FIGURE 4.2 *Distribution (%) of stage and grade by age category in patients with superficial TCC of the bladder*

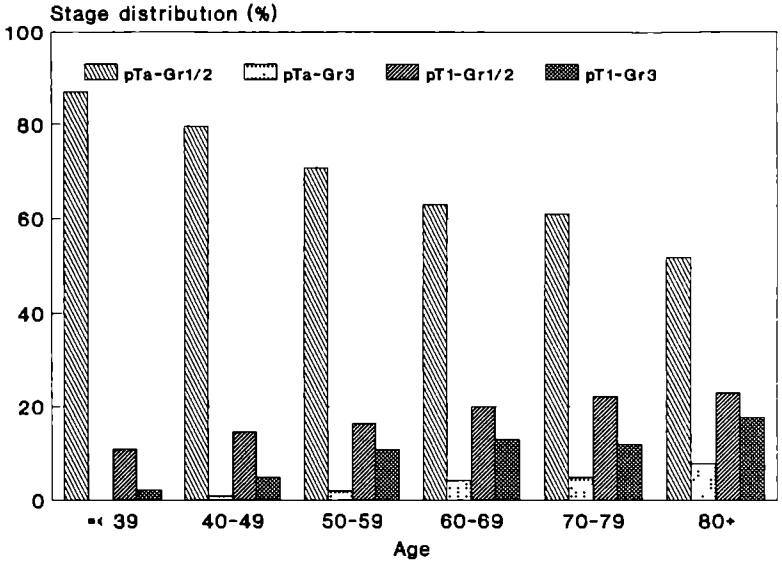
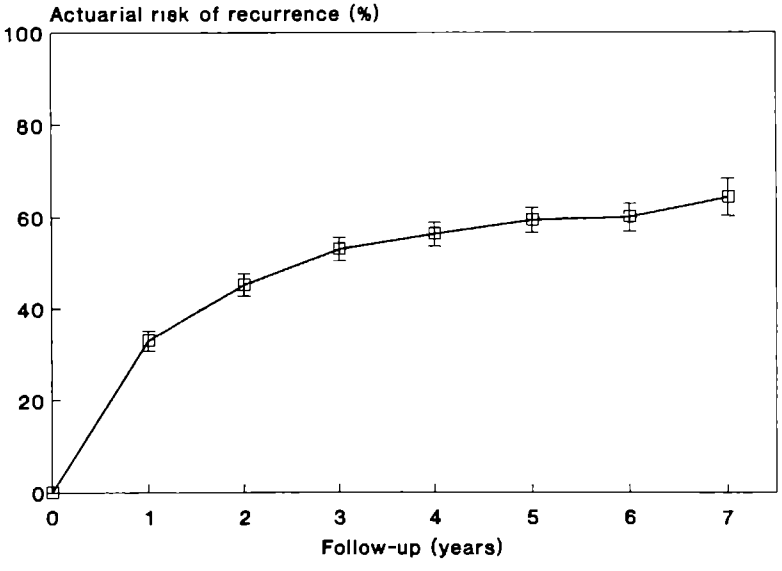


FIGURE 4.3 *Actuarial risk (%) of recurrent disease in patients with superficial TCC of the bladder (with 95% confidence interval)*



No. of patients is 1,722 (cystectomy patients excluded)

(multiple vs. solitary) and extent of the tumour (involvement of more than 1 bladder area vs. 1 area) had statistically significant effects on the risk of recurrence (all log-rank tests yielded P values < 0.001). In our study, the risk of recurrence was not significantly different in male and female patients ($P = 0.56$) and in patients younger and older than 70 years of age ($P = 0.93$).

Even though intravesical chemotherapy or BCG was applied more frequently in patients with a poor prognostic profile, adjuvant therapy proved to be effective for preventing recurrences. In the patients who were treated with TUR alone, the 3-year risk of recurrence was 55%, whereas this risk was 49% ($P = 0.005$) in the cases treated with intravesical instillations.

We subsequently re-evaluated all the factors in a multivariate proportional hazards regression model. In this model, we also adjusted for the potential distorting effect of adjuvant intravesical chemotherapy. The results remained practically the same compared to those from the univariate analyses. Tumour stage, grade, extent and multiplicity had statistically significant independent prognostic value regarding the risk of first recurrence. See Table 4.2.

TABLE 4.2 *Results of the multivariate proportional hazards regression model on the risk of first recurrence*

Factor	Relative Risk	95% Confidence Interval
Sex		
Male vs. female	1 01	0 84 - 1.21
Age		
≥ 70 vs. < 70	0 92	0 80 - 1.06
Tumour stage		
pT1 vs. pTa	1 38	1 16 - 1.65
Tumour grade		
2 or 3 vs. 1	1.22	1.04 - 1.43
Tumour extent		
≥ 2 areas vs. 1	1.34	1.14 - 1.57
Multiplicity		
Multiple vs. solitary	1.42	1.21 - 1.67
Therapy		
Instillations vs. TUR alone	0.67	0.57 - 0.80

Patients with the most favourable prognostic profile may therefore be defined as those with a solitary pTa grade 1 tumour located in just one area. In our study cohort, 390 patients had such a favourable score on all four factors. The 3-year risk in this group of patients (20% of whom were treated with

intravesical instillations) was 37%. In the prognostically least favourable group of 55 patients with multiple pT1 grade 3 tumours located in more than one area, the 3-year risk was as high as 77%, even though 69% of these patients were treated adjuvantly.

Progression

In the documentation project, disease progression was defined as a shift to a higher stage category (or the development of metastases). The three-year actuarial risk of progressive disease was 10.2% (95% CI: 8.6-11.8%). After five years, this risk had hardly increased: 13.3%. As is the case with the risk of recurrence, tumour stage, grade, extent and multiplicity appeared to have prognostic significance for the risk of progression. Furthermore, the three-year risk in patients older than 70 years was 12.7%, whereas this risk was only 7.4% in patients younger than 70 years of age (P = 0.001). Contrary to the effect on recurrence, intravesical instillations did not lower the risk of progression. Because the group of patients who received adjuvant therapy had a poorer prognostic profile, the risk of progression in this group was even higher than in the patients treated with TUR alone (12% versus 8%).
Except for tumour extent, all the factors with prognostic value in the univariate analyses retained their statistically significant quality in the multivariate regression model.

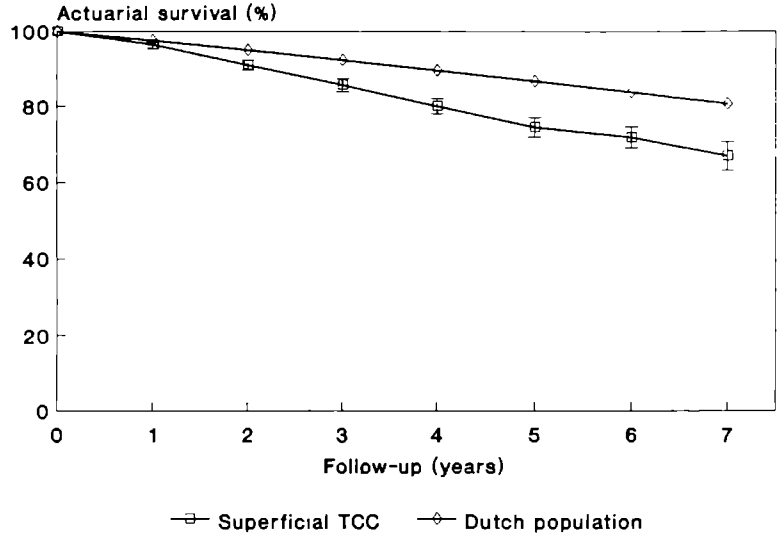
Survival

The actuarial risk of dying within 5 years after diagnosis was 25% (95% CI: 23-27%). See Figure 4.4. This risk has to be compared to the expected risk of dying from all causes given the age and sex distribution of this group of patients. Using data from the Registration of Causes of Death from the Dutch Central Bureau of Statistics, we calculated the expected risk to be 13%. Therefore, the relative 5-year survival of patients with superficial bladder cancer was (100-25) / (100-13) = 86%. Thus, the excess risk of dying within 5 years was approximately 14%.

DISCUSSION

The reported distributions of disease characteristics at initial diagnosis in our patients with primary superficial TCC, may not be representative for the situation in other countries. Especially the distribution of tumour grade and cold biopsy results may differ because there are not yet any objective criteria available to enable all pathologists to classify urothelium specimens in a reproducible manner.[16,23,25] Although the stage distribution is believed to be a better measure for comparison, different interpretations of the pT category by different pathologists are also possible.[1,14,17,22] Another factor which very often influences the distribution of disease characteristics is the inclusion of patients with recurrent instead of primary disease.

FIGURE 4.4 *Actuarial survival (%) in patients with superficial TCC of the bladder (with 95% confidence interval) compared to the Dutch population (adjusted for differences in age and sex distribution)*



Over the past 15 years, it is likely that an increasing number of "papillomas" have been classified as papillocarcinomas (until 1978, the UICC listed only the category pT1 for superficial bladder cancer).[29] For this reason, comparison with other case series is only worthwhile if these series were documented fairly recently. In a recent study by Abel, 107 (62.6%) out of the 171 cases with bladder cancer had superficial disease at presentation.[2] Of these, 71% were classified as pTa. From the total group, 60.7% (compared to 70.1% in our study) had solitary tumours. Grades 1, 2 and 3 accounted for 6.5%, 85.0% and 8.4% of all the tumours, respectively. This distribution, which is very different from the finding in our study, illustrates the need for better reproducible methods for the assessment of certain indicators used for prognosis. In a recent Danish study, 61% of 500 bladder cancer cases had superficial disease, of whom 69% had stage pTa.[31] These numbers are very similar to those in our study. In the Danish case series, 7.9% of the pTa/pT1 patients had carcinoma in situ in the cold-cup biopsy specimens taken at the first presentation of disease. Another 15.4% showed atypia grade 2. In a study by Flamm and Dona, CIS was found in the quadrant biopsy specimens in 6% of 216 patients. Dysplasia was found in 18%.[8] In our study, the corresponding percentages were 8.2 and 13.6, respectively. In a recent study by Solsona,[28] 48 out of the 306 patients with superficial bladder tumours had associated

carcinoma in situ, but this high number was caused by the inclusion of random area as well as suspicious area biopsies.

Nearly 60% of all the patients in our study had at least one recurrence within 5 years; most of them within 2 years (two-year recurrence risk: 45%). In fact, the recurrence risk in superficial bladder cancer is so high that (as apposed to other cancer sites) a second occurrence of TCC in the bladder is always interpreted as a recurrence, although this is theoretically incorrect.[3] The recurrence risk is dependent on a number of prognostic factors.[3,19] In our case series, we studied the effect of six prognostic factors and found that tumour stage, grade, extent and multiplicity were statistically significant prognostic indicators. Using these indicators, it may be possible to discern groups of patients with very different risks of recurrence. This, however, does not mean that it will be possible to predict the risk for individual patients fairly accurately. After all, for an individual patient there are only two possible outcomes: either he suffers a recurrence or he does not. Until we are able to differentiate all superficial bladder cancer patients into one group with a 100% recurrence risk and one group with a 0% recurrence risk, predictions for individuals will always be inaccurate.[18] The finding in our project that even the best prognostic group still had a three-year recurrence risk of 37%, rather than 0%, shows that the inaccurate measurement of prognostic indicators together with biological variability inevitably leads to inaccurate predictions. Although we have a number of highly significant prognostic indicators for the risk of recurrence, apparently we do not have enough of these indicators yet.

Superficial bladder cancer patients have a relatively high survival rate. In our study, the five-year survival was 75%, compared to 87% for the Dutch population adjusted for age, sex and calendar period. This finding is very similar to the 88% five-year survival rate for early stage bladder cancer (adjusted for normal life-expectancy) in the USA.[4] In a recent study in the United Kingdom, the five-year survival in 150 pTa and 85 pT1 patients was 80 and 69%, respectively.[10] Flamm and Havelec[9] found a tumour-related mortality rate of 12.5% in 345 patients with primary superficial TCC treated with TUR and intravesical instillations.

Despite the fact that the excess mortality in superficial bladder cancer is small, it may be asked why there is any excess mortality at all. Theoretically, it is possible that some of the superficial bladder cancers were already higher stage cancers at initial diagnosis. It is not exceptional for the pathologist to receive a resection specimen that does not contain any muscle tissue. Thus, some T2 tumours (with a poorer prognosis) may have been staged as pT1 tumours. In the surveillance programme of the U.S.A. National Bladder Cancer Collaborative Group, for example, there was no muscle tissue present in the specimens of 40 out of the 95 tumours classified as pT1.[6] By contrast, in a recent study by Abel *et al.*,[1] muscle tissue was present in 95% of the pTa/pT1

biopsy specimens. Unfortunately, comparable information was not available in our project.

Another possible explanation for excess mortality is undertreatment. Especially multiple high grade tumours which extend into the lamina propria are often seen to progress to higher stage disease.[6,11,24] But until now, this knowledge has not led to a consensus policy of treating all "high risk" tumours with (at least) intravesical instillations. According to our data, a surprisingly high number (26%) of patients with multiple pT1 grade 3 tumours were treated with TUR only. Nevertheless, it is dubious whether intravesical instillations prevent progression. Intravesical chemotherapy will usually decrease the rate and number of recurrences, but according to many authors it does not necessarily alter the ultimate outcome of the disease.[9,12,21,27,30]

TABLE 4.3 *Influence of the use of intravesical instillations for the treatment of the primary tumour on the five-year actuarial risk of progressive disease*[#]

	5-year risk of progressive disease (%)				
N=1674	TUR only		Intravesical instillations		Log-rank P value
Sex					
Male	11.1	(N=902)	14.7	(N=499)	0.05
Female	11.0	(N=214)	19 6	(N=109)	0.06
Age					
< 70	9.1	(N=634)	14.5	(N=314)	0.01
≥ 70	13.6	(N=482)	17.0	(N=244)	0.29
Stage					
pTa	8.3	(N=840)	10.1	(N=339)	0.66
pT1	19.3	(N=276)	24.7	(N=219)	0.07
Grade					
1	4.1	(N=531)	7.7	(N=137)	0.29
2	15.9	(N=495)	12.0	(N=277)	0.24
3	25.3	(N= 90)	32.2	(N=144)	0.29
Multiplicity					
Solitary	8.8	(N=856)	10.4	(N=325)	0.27
Multiple	18.6	(N=254)	24.1	(N=229)	0.32

[#] *Progressive disease is defined as any shift to a higher stage category or the development of metastases*

Our data support the observation of these authors. As Table 4.3 illustrates, intravesical instillations seem to increase rather than decrease the five-year risk of progressive disease. However, this finding was caused by the fact that

more patients with a relatively poor prognosis received adjuvant therapy. In a proportional hazards model with sex, age, tumour stage, grade, multiplicity and therapy, the relative risk of TUR-only versus intravesical instillations was 1.0 (95% CI: 0.7-1.3) Nevertheless, even though analysed multivariately, this finding has to be interpreted with caution because our study was not initiated to study therapy effects and therefore was not randomised. Furthermore, most of the patients in our study who were treated adjuvantly, received intravesical instillations with Adriamycin or Mitomycin-C Intravesical immunotherapy with Bacillus Calmette-Guérin RIVM, a strain produced by the Dutch National Institute of Public Health and Environmental Hygiene, was applied less frequently Two recent studies give some indication that BCG may be more effective in preventing progression than the chemotherapeutical agents.[7,15] Also, at the present time an EORTC phase II study is going on in which a sequential combination of intravesical chemotherapy with Mitomycin-C and intravesical immunotherapy with BCG is evaluated in recurrent superficial TCC of the bladder. Possibly, in the near future such a combination regimen may appear to be effective in delaying or preventing disease progression

In summary, we can conclude that even superficial TCC, as a distinct subgroup of bladder cancer, is a heterogeneous disease with an unpredictable clinical course. Even though some important indicators for future recurrences and progressive disease can be identified (such as tumour stage, grade and multiplicity), it remains a challenge to find more and stronger prognosticators which can more accurately predict the disease outcome in individual patients. Only then will it be possible to treat patients with a poor prognosis more aggressively and to avoid overtreatment of patients with a fairly good prognosis.

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CHAPTER 5

PROGNOSTIC FACTORS IN SUPERFICIAL BLADDER CANCER. A REVIEW

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INTRODUCTION

Cancer statistics in the USA show that in 1990, cancer of the urinary bladder accounted for 1.9% of all cancer-related deaths (9,700 deaths/year); 4.7% of newly diagnosed cancers were located in the bladder (49,000/year).[1] Bladder cancer is a disease of the elderly, with a male predominance (4:1). The majority of bladder tumours present as superficial transitional cell carcinomas (TCC, pTa-1, grades 1-3). Approximately 60% of endoscopically resected superficial bladder tumours recur, usually within 1 year;[2] 10-20% of superficial TCC show progression to invasive and/or metastatic cancer.[3]

Although all superficial TCCs are considered to be low-stage disease, they still comprise a heterogeneous group of tumours. A minority of patients have a relatively benign type of tumour which does not recur after transurethral resection (TURT). In these patients adjuvant treatment seems to be unnecessary. The largest group consists of patients who develop recurrent superficial bladder cancer without progression. A small group of patients, however, already have relatively malignant superficial tumours at presentation and develop muscle invasion despite adjuvant intravesical treatment. Cutler and associates hypothesised that 25% of all superficial bladder tumours are 'aggressive' tumours from the start.[4] It is important to distinguish these patients as early as possible. Many prognostic factors which might aid in this selection have been described over the past decades, but none of them is able to predict recurrence or progression with any real accuracy. In this paper the current knowledge about prognostic factors in superficial TCC of the bladder is reviewed.

CLINICAL FACTORS

Bladder cancer in the first decades of life carries a relatively good prognosis. This can be explained by the fact that bladder cancer at a young age is usually diagnosed as low-stage disease.[5] Within the older age groups, however, age may affect survival to some extent, but the evidence is not very strong.[6-8] Probably, the prognostic significance of age is entirely determined by its correlation with tumour stage and grade.[9] Sex has never been found to be an important prognostic factor in superficial bladder cancer.

The recurrence rate of superficial bladder tumours established before adjuvant treatment is initiated, has a significant impact on future recurrence and progression.[4,10-12] Cutler and associates studied 404 patients with newly diagnosed bladder cancer and 446 patients with recurrent bladder cancer.[4] They found that the average time interval between the first and second recurrence (13 months, 93 patients), or between the second and third recurrence (12 months, 48 patients) was markedly shorter than that from the initial diagnosis to first recurrence (31 months, 233 patients). Dalesio et al.

found that the recurrence rate (the number of follow-up cystoscopy studies at which a recurrence was noted divided by the total number of months of follow-up) in 190 patients with primary tumours was 5.2 compared to 10.1 ($p<0.001$) in 118 patients with recurrent tumours.[10] They also found that patients with less than one recurrence per year when they entered the study had a similar prognosis to that of patients with a primary tumour. Loening et al. studied eight prognostic factors in 178 patients and found that in patients with a history of bladder cancer only the pretreatment recurrence rate had any influence on the later recurrence rate.[11] In a retrospective study by Lutzeyer and colleagues on 315 patients, recurrences were noted in 45% of the patients within 3 years and were followed by a second recurrence in 84%.[12] Tumour progression was observed in 20-25% of primary pTa-pT1 tumours, whereas 56% of recurrent pT1 tumours progressed.

Tumour multiplicity is generally accepted as an important risk factor for a higher recurrence rate[4,10,12,17] and progression.[12,14] Dalesio studied 308 patients with pT1 bladder cancer who were treated with TURT and intravesical instillations. In a multivariate analysis, the number of tumours was the most important prognostic factor: 161 patients with 1 tumour had a recurrence rate of 4.8, 71 patients with 2-3 tumours had a recurrence rate of 7.8 and 68 patients with more than 3 tumours had a recurrence rate of 12.3.[10] The British Medical Research Council found similar results in a multivariate analysis of 305 patients with superficial bladder cancer: the 2-year risk of recurrence for 91 patients with a single tumour was 31%, for 214 patients with multiple tumours this was 58% ($p<0.001$).[15]

The size of the tumour also seems to have prognostic value,[4,6,7,10,11,13-15] although the 'critical' size of a tumour differs from study to study. Tumour localisation was found to be of importance in some studies. In the study by Loening, patients with a tumour in the trigone tended to have a shorter disease-free interval than those without trigonal involvement, but this was not statistically significant.[11] Stephenson et al. found significant differences among subsites of the bladder.[18] Tumours in the bladder neck ($n=101$) had a significantly poorer prognosis (5-year survival of 39%, compared to 50-56% for other subsites, $p<0.01$). Localisation in the dome ($n=70$) was associated with higher grade lesions ($p<0.001$). However, although Stephenson's study incorporated a large number of patients (914), the absence of any correction for other prognostic factors makes these results difficult to interpret.

Response to intravesical instillations also gives important information.[15,19] Recurrent tumour 3 months after intravesical instillations was the most important prognostic factor in a multivariate analysis conducted by Parmar et al.: in 258 patients with a negative urethrocystoscopy (UCS) at 3 months, the 2-year recurrence rate was 34%, while in 47 patients with positive findings at UCS this was 70% ($p<0.001$).[15] Herr found similar results in a group of 221

patients with superficial bladder cancer treated with TURT and Bacillus Calmette-Guérin (BCG).[19] If a pT1 lesion was found, three months after BCG therapy, the risk of progression was 82% (14/17 patients), with a median interval of only 8.4 months, compared to 25% (44/178 patients) after a median period of more than 5 years in patients with no tumour or a pTa tumour after 3 months.

In conclusion, recurrence rate established before adjuvant treatment, recurrent tumour after adjuvant treatment and tumour multiplicity are important prognostic factors. Tumour size and localisation may also have some prognostic value.

HISTOPATHOLOGICAL FACTORS

High grade tumours appear to have a higher risk of recurrence[4,10,11] and progression[4,6,7,12,13,20-23] and carry a higher risk of bladder cancer-related death.[8] Flamm and Havelec retrospectively studied the 5-year tumour-related mortality in a multivariate analysis. They found that poor differentiation was an important prognostic factor: 26/286 deaths occurred in grade 1 and 2 lesions, versus 14/59 in grade 3 ($p=0.04$).[22] However, the interpretation of tumour grade may differ between pathologists. Parmar et al. found that tumour grade was a prognostic factor when assessed by a reference pathologist, but that it was of no prognostic value when assessed by local pathologists (Table 5.1).[15] Ooms et al. compared the grading results of 57 bladder tumours by 7 pathologists and found an inconsistency of about 50% among pathologists (interobserver variability) and for individual pathologists across time (intra-observer variability).[24]

Tumour stage also has prognostic significance,[4,6-8,11-14,21,23,25] but again, the limitations of the histological classification should be taken into account (Table 5.1). Cutler et al. found that 25% of the patients with pT1 tumours (and 40% with pT1 grade 3 tumours) developed muscle invasion within two years as compared to 3% of the patients with pTa tumours.[4] In a multivariate regression analysis, Loening and associates found that tumour stage had a statistically significant relation with the recurrence rate in patients with no bladder cancer history (hazard ratio = 1.6).[11] Malmstrom et al. studied the clinical course in 195 patients. Tumour stage appeared to be the most significant predictor of cancer-related death in a multivariate analysis.[8] Other studies also found that tumour stage was the most significant determinant for survival[7,25] and cancer-related death.[21]

The presence of histological abnormalities adjacent to the tumour seems to be a positive predictor for subsequent tumour progression.[26] Random bladder

biopsies can give information about concomitant macroscopically invisible abnormalities of the urothelium, which might also influence the prognosis. However, urologists should be aware of the imprecision and lack of reproducibility with regard to the interpretation of such biopsies.[27] There is a correlation between the appearance of the mucosa at cystoscopy and the histology of the biopsy. Wallace et al. studied 585 mucosal biopsies in 154 patients.[28] All the carcinomas, whether carcinoma in situ (CIS), papillary or invasive carcinoma, were grouped together. In 399 biopsies of normal-looking mucosa, histological abnormalities were found in 33%, including carcinoma in 4.5%. In 98 biopsies of red but flat mucosa, abnormalities were found in 52%, including carcinoma in 14%. In 88 biopsies of granular or mossy mucosa, these figures were 81.5% and 42%, respectively. Random biopsies are taken from normal-looking mucosa. An abnormal biopsy result (dysplasia and/or CIS) suggests a higher risk of recurrence[4,14,20,29] and progression.[4,13] These studies, however, involved small numbers of patients (58-216) and had limited follow-up periods (1.6-3 years). Furthermore, the relation between the biopsy result and the risk of recurrence was not adjusted for other prognostic factors, even though the result of random biopsies is known to be strongly correlated with tumour stage and tumour grade.[29-30]

TABLE 5.1 *Difference in the prognostic value of tumor grade and stage as assessed by reference or local pathologist*[14]

	Patients	2-year recurrence rate, %	p value (log rank)
Reference pathologist			
Grade 1	188	36	
Grade 2	91	38	0.009
Grade 3	26	70	
pTa	254	37	0.11
pT1	51	48	
Local pathologist			
Grade 1	182	37	
Grade 2	110	43	0.4
Grade 3	13	30	
pTa	151	32	0.02
pT1	154	46	

Urine cytology is a useful routine and noninvasive test for the early detection of bladder cancer and for monitoring a patient after treatment, although its accuracy depends on the tumour grade and the experience of the cytopathologist.[31-33] The use of monoclonal antibodies in urine cytology might increase its accuracy.[32] The prognostic value of cytology is questionable, although Heney et al. found a 3-year disease-free survival of more than 50% in 113 patients with negative cytology compared to a disease-free survival of less than 25% in 39 patients with positive cytology ($p < 0.01$).[13]

In conclusion, tumour stage and especially tumour grade are major histopathological prognostic determinants, even though there is considerable variability in the classification of these factors. The value of random mucosal biopsies remains controversial. Urine cytology is useful for diagnosis, but probably has no prognostic value.

BLOOD GROUP ANTIGENS

In the late seventies, a relation was reported between a loss of cell surface ABH blood group antigens (BGA) and urothelial malignancy. Loss of BGA expression indicated tumour cell dedifferentiation and hence carried a poor prognosis.[34] In 1979, Emmott et al. published data on the BGA status of 76 bladder tumours.[35] They found that 70% of grade 1 lesions were BGA positive, compared to none of the 26 grade 3 tumours. None of the 48 invasive tumours were positive, compared to 12 of the 16 stage A tumours. Of the 9 superficial tumours which progressed, only 1 was BGA positive. Other studies found similar results: the absence of BGA was associated with a markedly higher risk of progression in muscle invasion.[36-38]

These initially promising results, however, were followed by less positive and even contradictory reports. Fujita and associates found that 43% of grade 3 tumours, 43% of invasive tumours and 60% of metastatic tumours retained the isoantigen, and concluded that it was an invalid predictive indicator.[39] It was only possible to detect all grade 2 or 3 tumours and all invasive tumours if the patients had blood group A or B, and there was H but no A and B activity (a total blockade of the conversion of H substance into A and B substances). Pauwels et al. analyzed 78 TCCs of the bladder.[40] In 51% of the 59 superficial tumours, BGAs were present, whereas all 19 infiltrating and high grade tumours were negative ($p = 0.001$). However, in superficial tumours no correlation was found between antigen expression and tumour recurrence or progression: the mode of BGA expression had no additional prognostic value to tumour grade.

Nakatsu et al. investigated immunoperoxidase detection of BGA and carcinoembryonic antigen (CEA) on preserved paraffin blocks of histo-

pathologically verified pT1 and pT2 TCC.[41] Absence of BGA was not correlated with histological grade and stage, but the presence of CEA was. BGA could not predict poor survival, whereas CEA detection could. In a prospective study with a 3-year follow-up, Abel et al. studied the prognostic value of BGA expression.[42] They precluded the use of BGA as a guide to prognosis when used alone or in combination with the pathological stage.

ABH antigenicity of mucosal biopsies has also been studied.[17,23] In a small series, Das and colleagues found that ABH antigenicity was a significant predictor of recurrent disease: in 21 patients with antigen-positive mucosal biopsies, the recurrence rate was 0.3 per year compared to 2.0 in 13 negative patients ($p < 0.001$).[17] Its predictive value was better than that of number, size, grade and ABH antigenicity of the primary tumour. Huland et al. found similar results.[23] Loss of BGA was found in 7 tumours and 5 biopsies in 8 patients who developed progression, compared to 5 tumours and 5 biopsies in 14 patients with non-progressive tumours.

The possibility that ABH isoantigen change is an early event in bladder carcinoma, together with the assumption that bladder carcinoma is a heterogeneous disease might be an explanation for these controversial findings. The limited value of the ABH blood group antigen expression and its failure in blood group O individuals, encouraged the evaluation of other blood group related antigens. For example, in a group of 93 tumours, a relation was found between an abnormal pattern of the Lewis A antigen and tumour stage and grade ($p < 0.01$).[43] Lewis X antigen can be used on exfoliated bladder cells and enhances the detection of urothelial tumour cells, particularly from low stage and low grade tumours.[44]

In conclusion, it is not yet clear whether or not the expression of blood-group-related antigens has any additional prognostic value to the prognostic characteristics already available.

CYTOGENETIC FACTORS

It has been hypothesised that disease progression is associated with genomic instability. Therefore, measurement of the DNA content (ploidy analysis) may be of use to determine progression. DNA ploidy seems to be an important marker in predicting tumour behaviour. Highly aneuploid tumors of the bladder have a strong propensity to progress to invasive and metastatic growth. A small proportion of grade 2 and 3 tumors have a predominantly tetraploid DNA distribution and this pattern appears to express an intermediate grade of clinical malignancy, with a high recurrence rate and a moderate invasive tendency.[45] The diagnostic accuracy of the DNA ploidy and its value for predicting recurrence can be increased especially when determined by flow

cytometry.[45,46] Recently, chromosome abnormalities have been examined with in situ hybridisation, a new and rapid technique, which assesses DNA ploidy even more specifically than flow cytometry.[47]

Lamb was one of the first to report on a large series of bladder tumours in which a correlation was found between histopathology and chromosome counts.[48] When cellular differentiation was lost, this was associated with a change in the average number of chromosomes in the tumour. He also found a wider range of chromosome numbers among the individual tumour cells and an increase in structural chromosome abnormalities. Later on, more studies confirmed the importance of DNA ploidy. Masters et al. found that tumour aneuploidy had similar prognostic significance to high tumour grade and a high proportion of tumour cell nuclei in the proliferative S phase.[49] Progression occurred in 35% of the patients with one of these 3 features within 3 years. All of these features were found in 8 tumours, 6 of which became invasive. In a retrospective study on 195 evaluable patients, Malmstrom et al. found that ABH status and DNA ploidy had no significant value in a Cox multivariate analysis.[8] However, a combination of both factors was an independent predictor of early tumour progression in addition to tumour stage. Pauwels and associates also found a consistant correlation between chromosome numbers, tumour grade and stage and the clinical course. Chromosome abnormalities, however, were of no additional prognostic value to grading.[40]

DNA ploidy has also been investigated in superficial bladder cancer. DeVere-White et al. found that tumour aneuploidy in pTa grades 1-2 bladder tumours was closely related to disease recurrence and progression: 6/21 patients with a diploid-tetraploid <20% hyperdiploid histogram developed recurrent tumours, compared to 9/9 patients with a nontetraploid-aneuploid, a tetraploid-aneuploid, or a diploid-tetraploid > 20% hyperdiploid histogram. Also, the ploidy pattern changed during recurrent disease in 20/28 cases.[50] This gave additional prognostic information to stage and grade classification.

In an earlier study using flow cytometry, Norming et al. found the same DNA ploidy in random mucosal biopsies and exophytic tumours, which supported the concept that despite normal morphology, intraurothelial lesions might develop into frank tumours.[51] Histopathology and DNA flow cytometry of random mucosal biopsies were also compared in 290 patients with untreated bladder carcinoma.[52] There was a clear relation between histopathology and DNA ploidy. Biopsies with CIS, atypia or no atypia showed aneuploidy in 76%, 41% and 10%, respectively. The DNA profiles of the aneuploid cell populations, however, were similar, irrespective of the corresponding histopathology. These findings suggest that apart from ploidy, other factors, such as the DNA profile, may appear at an early stage of tumour development.

The volume corrected mitotic index (M/V index) also carries prognostic value.[21] In a series of 83 bladder cancer patients with a mean follow-up of 13 years, the M/V index correlated with disease recurrence, survival and metastatic potential. In a multivariate analysis with tumour stage and grade, the M/V index had statistically significant prognostic value.

Marker chromosomes are abnormal morphological forms, which are thought to occur in diseases which predispose to cancer. Some reports describe that recurrences[53-55] and progression[56] in moderately and well-differentiated superficial bladder tumours only occur in marker chromosome positive tumours. An absence of marker chromosomes, however, had no prognostic value. Falor and Ward studied a small series of patients and stated that the triad of tetraploidy, marker chromosomes and submucosal invasive carcinoma appeared to carry such a lethal prognosis that it justified early radical cystectomy: out of 6 patients with this combination, 3 required cystectomy 9-25 months after diagnosis and 3 patients (1 after cystectomy) died from metastatic disease within 28 months.[53] Sandberg found marker chromosomes in 32 out of 50 papillary tumours.[55] In 12 recurrent tumours, only one was marker chromosome negative. In invasive TCC, a correlation was seen between the numbers of marker chromosomes and progression. More recently, the additional value of marker chromosomes to histopathology could not be confirmed. In a study on 50 patients with a maximal follow-up of 17 years, Falor and Ward-Skinner found that absence of marker chromosomes did not rule out ultimate recurrence and in cases with recurrence, the marker chromosome was of no additional value to histopathology.[57]

Chromosome abnormalities may be the cause of malignant transformation, or may be caused by disease progression or selection because of drug resistance. If a cell culture is used, its influence on chromosomal structures has to be taken into account. Deletions in chromosome 1 are common in tumours at most sites, also in bladder cancer, indicating that it may be an early event in malignant transformation.[58] Deletions in chromosome 11[58,61] and 17[59] have been identified as poor prognostic factors in bladder cancer. Loss of genetic material from the short arm of chromosome 11 might be related to invasive behaviour of a tumour.[61] Deletions in 11p might be of special interest in view of the identification of the c-Ha-ras1 oncogene on this chromosome arm.[58] In this case, homozygosity for recessive cancer genes might explain the relation between the loss of chromosomal material and cancer. With the recent identification of the transformation-associated p53 gene as a tumour suppressor gene, located on chromosome 17,[62] a possible relation has been found between p53 function and invasive behaviour of TCC. Deletion in chromosome 9 is seen in all stages of bladder cancer, which suggests that the loss of a tumour suppressor gene on chromosome 9 might be an early event in malignant transformation.[59,63] It is intriguing to note that the genes which determine the ABH surface membrane antigenes are also located on chromosome 9 and that

the loss of ABH antigen expression may also be associated with an increased risk of tumour progression. Other important primary chromosomal changes may be trisomy 13 and trisomy 7.[64] Several other chromosome abnormalities have been detected, but no definite correlation has yet been found with bladder cancer.[64-68] Furthermore, Perucca et al. emphasized that there is considerable variability among different publications regarding the prevalence of chromosome abnormalities.[68] Nevertheless, several cytogenetic as well as molecular findings have provided evidence that genetic deletions (existence of tumour suppressor genes) are involved in tumour progression.

BIOCHEMICAL FACTORS AND TUMOUR-ASSOCIATED ANTIGENS

Cell motility and extracellular matrix (ECM) degradation are thought to be important factors in the process of tumour invasion and/or metastases. The autocrine motility factor (AMF) is a cytokine which stimulates the motility of human tumour cells and may play a major role when tumour cells become locally invasive.[69] AMF can be measured in the urine. Motility values (mean motility) are higher in bladder cancer patients (197.3, 22 patients) than in healthy controls (47.3, 27 patients, $p<0.001$) and a correlation has been found between mean motility and tumour stage (135.4 in noninvasive TCC versus 229.3 in invasive TCC, $p<0.001$) and recurrence rate (228.2 in patients with recurrences versus 71.7 in tumour-free patients, $p<0.001$).[70] Plasmin plays an important role in ECM degradation. Plasmin degrades some components of the ECM and activates two important enzymes which degrade fibrillar collagen and collagen in the basement membrane. The levels of plasminogen activator (which transforms plasminogen into plasmin) were found to be higher in bladder cancer than in normal mucosa.[71] Moreover, the levels increased with histological grade. Further studies must identify the prognostic significance of AMF and ECM degradation.

Immunohistochemical staining of subepithelial basement membrane components can clearly show any interruption or absence of this membrane, which is of value for the early detection of microinvasion. In patients with a patchy or absent basement membrane the incidence of progression was significantly higher, but there was no relation with the recurrence rate.[25,72] However, in a multivariate analysis, the value of basement membrane staining was largely eliminated by tumour stage.[25]

The value of the epidermal growth factor receptor (EGF-R) has been investigated recently.[73,74] Normally, EGF-R is found only on the basal layer of epithelial cells. In bladder tumours, the urinary concentration of EGF and the EGF-R expression in tumours may be elevated. Messing found that EGF-R was expressed on superficial and deeper layers of the urothelium in low and high grade TCC, as well as in normal-looking urothelium in patients with

TCC elsewhere in the bladder.[74] This might favour the interaction of premalignant and malignant urothelium with urinary EGF. Neal et al. studied 101 patients with newly diagnosed bladder cancer, with a follow-up of 30 months.[73] They found an association between strongly positive immunohistochemical staining of the EGF-R (48 tumours) and high stage bladder cancer ($p<0.001$). In cases with pTa and pT1 bladder cancer (52 patients), EGF-R positivity was associated with multiplicity, short time to recurrence and high recurrence rate. In a multivariate analysis, EGF-R positivity was predictive of bladder-cancer-related death in all 101 patients (relative risk 3.4, $p<0.001$). In 52 patients with superficial TCCs, EGF-R positivity was predictive for time to recurrence (relative risk 2.3, $p=0.03$) and time to progression (relative risk 22.12, $p<0.001$).

Elevated plasma tissue polypeptide antigen (TPA) levels have been demonstrated in malignant and benign conditions. In all stages of bladder cancer, plasma TPA might be a sensitive diagnostic marker.[75-76] Urinary TPA was found to have a significant relation to the T category in a study on 81 bladder cancer patients: TPA levels were elevated in 74% of the patients with invasive bladder cancer, compared to 15% of the patients with superficial tumours ($p<0.001$).[77] In invasive bladder cancer, TPA can be used to monitor therapy.[78] However, the role of TPA in superficial bladder cancer is probably limited to the detection of recurrent disease and has no prognostic value.

Transferrin receptor (TFR) expression is considered to be a marker of proliferative activity. Smith et al. found that TFR positivity on the initial primary tumour had a significant relation with recurrence rate.[79]

Urinary CEA is useful for the early detection of bladder cancer and for monitoring treatment, but like urinary cytology, it probably does not carry any prognostic value. An increase in urinary immunoglobulins was found to be of negative prognostic value.[31]

Recently Fradet et al. showed that monoclonal antibody (Moab) T138, measured by flow cytometry, is a good single indicator of cancer progression, better even than tumour cell DNA ploidy.[80] The combination of both examinations might give additional information on the prognostic behaviour of bladder cancer. Several other Moabs have been used to stain TCC. Conn et al. used the Moab HMFG-2 to stain bladder tumours and mucosal biopsies.[81] In 76 bladder tumours, the staining pattern correlated with the tumour stage ($p<0.01$) and grade ($p=0.01$). In 35 mucosal biopsies, the staining pattern correlated well with the histopathology. The staining pattern also proved to be a good predictor of subsequent disease progression in superficial tumours.

CONCLUSIONS

Many prognostic factors have been reported for recurrence and progression of superficial bladder cancer. Unfortunately, however, in many reports the prognostic significance of a certain factor has been claimed with a (small) P value only, which has no quantitative meaning for the relevance of a factor This makes it rather difficult to make an objective interpretation of the results. Furthermore, many reports have only presented the results from univariate analyses, which may have led to overrated prognostic values (although a new factor which has prognostic significance only because of its correlation with other factors, may still be of practical use if it is cheap and easy to assess).

Which factors can be used in urological practice, or may be used in the near future to make a prognostic assessment and to define treatment policy? Recurrence rate before and after treatment gives important information about future tumour behaviour. Cystoscopic features, such as tumour multiplicity and size should also be taken into account. Although there is considerable variability in the interpretation of histopathological features, tumour grade and especially tumour stage are of major prognostic importance. Controversial reports about blood group antigens have made the ABH antigenicity tests unsuitable for daily practice. A correlation exists between DNA ploidy and the malignant potential of a tumour, but whether or not this information has any additional meaning to conventional histopathology remains to be proven The same applies to marker chromosomes and other chromosomal abnormalities Cell motility and ECM degradation are promising factors to study the malignant potential in an early phase, as is the EGF-R. Despite the identification of new prognostic factors, urologists have to be aware that their predictions of the clinical course in individual patients with superficial bladder cancer will not always be accurate

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CHAPTER 6

DYSPLASIA IN NORMAL-LOOKING UROTHELIUM INCREASES THE RISK OF TUMOR PROGRESSION IN PRIMARY SUPERFICIAL BLADDER CANCER

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SUMMARY

Random urothelium biopsies are frequently used as a prognostic test in the management of superficial bladder cancer. However, to our knowledge the prognostic significance of this test, in addition to the already available prognosticators, has never been studied. We prospectively assessed the clinical course of 1001 patients with primary superficial transitional cell carcinoma of the bladder from whom random urothelium biopsies had been taken at initial endoscopical surgery.

Actuarial risks of recurrence and disease progression were determined for each prognostic characteristic and comparisons were made using log-rank tests. The independent prognostic significance of random biopsies was examined with Cox's regression analyses.

The 3-year risk of recurrence in patients with dysplasia or carcinoma in situ (CIS) in macroscopically normal-looking urothelium was only slightly higher than the risk in patients without dysplastic changes (57% and 51%, respectively; $P = 0.09$). Concomitant dysplasia or CIS significantly increased the 3-year risk of disease progression (21% versus 7%; $P < 0.001$). After adjustment for the effects of age, tumor stage, grade, size and multicentricity, the result of random biopsies had no prognostic significance regarding the risk of recurrence, but the detection of dysplasia or CIS increased the risk of progression by a factor of 1.8.

This result suggests that random urothelium biopsies may be useful as an additional guide in defining therapy in primary superficial bladder cancer. However, before the implementation of routine random biopsies in clinical practice, their value should be evaluated by means of a medical decision analysis.

INTRODUCTION

The most common form of bladder cancer is papillary transitional cell carcinoma (TCC). These carcinomas are usually confined to the bladder mucosa or show superficial invasion into the lamina propria. It has been recognized for some time that at least part of these superficial tumors are manifestations of cystoscopically occult widespread urothelial disease. In these cases, urothelial dysplasia may be detected with random biopsies of normal-looking mucosa. In 1960 Eisenberg and associates were the first to show the clinical relevance of these concomitant dysplastic changes. Patients with cellular atypia in normal-looking mucosa had a poor prognosis, whereas patients with no mucosal atypia had controllable disease.[1] Since then, many authors have confirmed the prognostic significance of intraurothelial dysplasia in patients with superficial bladder cancer.[2 13]

It is well known that the presence or absence of dysplastic abnormalities strongly correlates with other prognostic factors, especially with tumor

grade.[5,11,14-16] To assess the independent prognostic significance of concomitant urothelial dysplasia, therefore, adjustment has to be made for this correlation with other factors. If the prognostic ability of the result of random biopsies is determined by its association with the factors already available, then random biopsies will be quite useless for patient management. However, apart from one small study on 37 patients with a pT1G3 tumor,[13] the existing prognostic factors have not been formally adjusted for in the studies on random biopsies published so far. We performed an analysis on the independent prognostic effect of concomitant dysplastic abnormalities in primary superficial bladder cancer regarding time to first recurrence (the term 'recurrence' in this text means a new tumor occurrence) and time to disease progression.

PATIENTS AND METHODS

The study cohort

Between January 1983 and December 1989, the Dutch South-East Cooperative Urological Group prospectively documented the patient and tumor characteristics of 1745 cases with histologically verified primary superficial TCC of the bladder. Superficial was defined as tumor extension limited to the mucosa (TNM stage pTa) or the lamina propria (pT1) of the bladder wall.[17] Because of its relatively aggressive behavior, primary carcinoma in situ (pTis: N = 52) was considered to be different from pTa and pT1 tumors and, therefore, was not included in this series. A proportion of the urologists who participated in the project took preselected cold-cup biopsies of normal-looking urothelium from all their patients during initial endoscopical surgery. The biopsy sites were the left and right lateral wall, the trigone and dome. The results of these biopsies were classified as being positive if dysplasia (either mild, moderate or severe) or carcinoma in situ (CIS) was found in one or more of the specimens. In 1044 patients, random biopsies were taken.

All the patients were initially treated with transurethral resection (TUR) of the tumor(s). Forty-three patients received additional treatment with interstitial radiotherapy, external radiotherapy or cystectomy because of residual tumor after TUR. These 43 patients were excluded from the analyses. Of the remaining 1001 patients, 607 were treated with TUR alone, and 394 received prophylactic adjuvant intravesical therapy (doxorubicin, mitomycin or bacille Calmette-Guérin). The patients were followed with cystourethroscopy and urinary cytology every three months for a period of one year. If there were no recurrences during this period, the patients were subsequently followed at 6-month intervals. Once yearly, follow-up data were registered concerning the disease status and vital status. In 1991, all the data from the project were reviewed using the medical files. The median follow-up period for the study cohort was 3.5 years.

Statistical methods

Time to recurrence and time to progression, calculated from the date of initial TUR, were used as end points in this study. Progression was defined as a shift to a higher tumor stage category or the development of regional or distant metastases. The follow-up of patients without tumor recurrence and disease progression was censored to the date of the last hospital visit. In case of death not related to the bladder cancer, the follow-up was censored to the date of death.

We used the actuarial method (with the log-rank test) to assess the prognostic effect of the following factors: age, gender, tumor stage (pT1 versus pTa), tumor grade (grade 3 versus 2 versus 1, according to the WHO grading system),[18] tumor multicentricity (multiple versus solitary), tumor extent and the result of random bladder biopsies (dysplasia or CIS versus normal). Tumor extent was defined as the number of bladder areas involved (3 or more versus 2 versus 1) instead of the size of the tumor. We distinguished the following bladder areas: bladder neck, trigone, dome, anterior and posterior wall, and left and right lateral wall.

The independent prognostic effect of dysplastic mucosa or CIS in random biopsy specimens on time to recurrence and time to progression was analyzed in multivariate analyses using the proportional hazards model.[19] In these multivariate analyses we first evaluated all the factors for inclusion in the model (with a stepwise procedure on level $P = 0.10$), except for the random biopsy result. In this first phase, we also took the therapy into account (intravesical chemotherapy or BCG versus TUR alone). Only after arriving at the final model we included the random biopsy result and tested the improvement of the model with the likelihood ratio test. The possibility of a different prognostic effect of random biopsies in subgroups of patients was tested by means of interaction factors (cross-product terms).

RESULTS

During the period of follow-up, 513 of the 1001 patients suffered at least one recurrence, 102 patients had a recurrence in a higher tumor stage category or developed regional or distant metastases. The results of the univariate analyses on prognostic factors for the risk of recurrence and the risk of progression are summarized in Tables 6.1 and 6.2, respectively.

The 3-year actuarial risk of recurrence in patients with dysplasia or carcinoma in situ in normal-looking urothelium was 57% (Table 6.1). In patients without these dysplastic abnormalities, the 3-year risk of recurrence was only slightly lower: 51%. This difference was borderline statistically significant ($P = 0.09$). Tumor stage, tumor extent, multicentricity and tumor grade were significant prognostic indicators for the risk of recurrence.

TABLE 6.1 *Univariate analysis of prognostic factors for tumor recurrence*

Factor	No.	3-yr risk of recurrence (actuarial)	P value (log-rank test)
Age			
0-49	90	0.49	0.96
50-59	178	0.52	
60-69	319	0.52	
70-79	306	0.54	
80+	108	0 51	
Gender			
Male	817	0.53	0.45
Female	184	0.48	
Tumor stage			
pTa	687	0.47	<0.001
pT1	314	0.64	
Tumor grade			
1	371	0 46	0.01
2	456	0.56	
3	174	0.56	
Tumor extent			
1 area	616	0.46	<0.001
2 areas	222	0.58	
3 or more	163	0.71	
Multicentricity			
Solitary	725	0.48	<0.001
Multiple	270	0.63	
Unknown	6		
Random biopsies			
Normal	793	0.51	0.09
Dysplasia/CIS	208	0.57	

The 3-year risk of tumor progression in patients with concomitant dysplastic abnormalities was much higher than that in patients with microscopically normal mucosa: 21% versus 7% ($P < 0.001$) (Table 6.2). As opposed to its effect on the risk of recurrence, the result of random biopsies was one of the most discriminating factors regarding the risk of progression. The same is true for tumor grade, which was strongly correlated with the result of random biopsies (the frequency of dysplastic abnormalities was 11%, 20% and 47% in patients with tumor grades 1, 2 and 3, respectively): whereas the risk of recurrence in patients with a tumor of grade 2 or 3 was identical, the risk of progression was much higher in patients with less differentiated tumors.

TABLE 6.2 *Univariate analysis of prognostic factors for disease progression*

Factor	No.	3-yr risk of progression (actuarial)	P value (log-rank test)
Age			
0-49	90	0 02	0.002
50-59	178	0.08	
60-69	319	0.09	
70-79	306	0.13	
80+	108	0.16	
Gender			
Male	817	0 09	0.35
Female	184	0.12	
Tumor stage			
pTa	687	0.07	<0 001
pT1	314	0.17	
Tumor grade			
1	371	0.04	<0.001
2	456	0.09	
3	174	0.26	
Tumor extent			
1 area	616	0.07	<0.001
2 areas	222	0.11	
3 or more	163	0.18	
Multicentricity			
Solitary	725	0.07	<0.001
Multiple	270	0.17	
Unknown	6		
Random biopsies			
Normal	793	0.07	<0.001
Dysplasia/CIS	208	0.21	

Another difference with regard to the risk of recurrence was that age appeared to be a prognostic indicator for tumor progression. Detection of superficial bladder cancer in older age groups was associated with a somewhat poorer prognosis.

After the univariate analyses, we used multivariate regression analyses to examine the independent prognostic effects of the factors listed in Tables 6.1 and 6.2. In these regression models we controlled for the effect of intravesical chemotherapy or BCG. Age was analyzed as a continuous variable (the number of years in relation to the mean age of 66). In the regression model of time to first recurrence, tumor stage, tumor extent and multicentricity had

statistically significant prognostic effects at the P = 0.10 level (Table 6.3). In this study, age, gender and tumor grade had no (statistically significant) independent prognostic value. The same held true for concomitant dysplasia or CIS. Adding the result of random biopsies to the model did not improve the model (-2 log likelihood = 0.93: P > 0.50). The hazard ratio of the random biopsy result was only 1.12 (90% CI: 0.93 - 1.34). Also, none of the interaction terms of the random biopsy result with other factors was statistically significant, indicating the absence of prognostic relevance of random biopsies in subgroups of patients.

TABLE 6.3 *Results of multivariate proportional hazards regression model of time to first recurrence*

Factor	Hazard Ratio	90% Confidence Interval
Tumor stage		
pT1 vs. pTa	1.51	1.30 - 1.75
Tumor extent		
2 areas vs. 1	1.19	0.97 - 1.45
3 or more areas vs. 1	1.68	1 36 - 2.08
Multicentricity		
Multiple vs. solitary	1.20	1.00 - 1.43
Therapy		
Instillations vs. TUR alone	0.70	0.60 - 0.83
Random biopsies		
Dysplasia/CIS vs. normal	1.12	0.93 - 1.34

The results of the model of time to progression are summarized in Table 6.4. Tumor grade appeared to be the strongest prognostic factor. The risk of tumor progression in the patients with a grade 3 tumor was more than 5 times higher than the risk in the patients with a grade 1 tumor. Other factors with predictive value for disease progression were age and multicentricity. In contrast to the effect on time to recurrence, random urothelium biopsies had additional prognostic relevance regarding time to progression (-2 log likelihood = 7.2: P < 0.01). The risk of tumor progression was increased by a factor of 1.8 (90% CI: 1.26 - 2.51) in the case of dysplastic abnormalities in apparently normal mucosa compared to a normal biopsy result. Inclusion of interaction factors led to no improvement in the model, indicating that the prognostic effect of mucosal abnormalities was approximately the same for different patient subgroups.

TABLE 6.4 *Results of multivariate proportional hazards regression model of time to progression*

Factor	Hazard Ratio	90% Confidence Interval
Age		
Each year in relation to 66 years	1 02	1 01 - 1 04
Tumor grade		
grade 2 vs. 1	2 12	1 28 - 3 49
grade 3 vs 1	5 47	3 29 - 9 12
Multicentricity		
Multiple vs solitary	1.82	1 31 - 2 53
Random biopsies		
Dysplasia/CIS vs normal	1 80	1 26 - 2 51

DISCUSSION

The coexistence of dysplastic abnormalities in normal-looking epithelium adjacent to urinary bladder tumors was first reported by Melicow in 1952.[20] In 10 total cystectomy specimens, cellular abnormalities were seen ranging from hyperplasia and dysplasia to carcinoma in situ. Five control tumor-free bladders, obtained from autopsy cases, showed only occasional cellular hyperplasia. Other histological examinations of cystectomy specimens[21 26] and of random mucosal biopsies in vivo,[14-16 27 31] have confirmed the high prevalence of atypia and carcinoma in situ in areas not cystoscopically suspected of harboring malignancy. In all the studies which examined the correlation with tumor grade, the frequency of dysplastic abnormalities was found to be higher in patients with less differentiated exophytic tumors. A correlation was also found with multicentricity and tumor stage.[11,16]

Eisenberg and associates were the first to evaluate the prognostic relevance of concomitant cytological changes in bladder biopsies.[1] Although random biopsies were taken from 53 patients with low stage tumors, the clinical course of only 24 of them was presented. Eight patients never showed any evidence of disease recurrence in an average of eight years of follow-up None of them had associated proliferative abnormalities. Seven patients, all with associated proliferative lesions, experienced therapy failure, with an average survival of 3 years. The remaining 9 patients (3 with associated proliferative lesions) survived for well over five years but suffered recurrent tumor formation. More recent studies confirmed the potential prognostic significance of random mucosal biopsies, both for tumor recurrence and tumor progression.[2 13] However, the results of some of these studies are difficult to

interpret because biopsies were not only taken at initial diagnosis but also during follow-up,[6] or because biopsies were also taken from macroscopically suspicious mucosa.[3,12] The results of these biopsy procedures are hardly comparable with those from biopsies from normal urothelium taken at initial diagnosis.[29] In addition, some of the studies were very small with patient numbers of less than 50.[4,8,9,12,13] The small study size is probably one of the reasons why none of the studies analyzed the independent prognostic effect of random biopsies in an unselected series of patients with superficial bladder cancer.

In newly diagnosed superficial bladder cancer, conventional histopathology (tumor stage and tumor grade) and some clinical factors (multicentricity and tumor size) are routinely used as prognostic factors.[32,33] It is not very likely that random urothelium biopsies will ever replace one or more of these factors, but they may be useful as an additional prognostic test. To our knowledge, the present study is the first to focus on the independent effect of dysplastic abnormalities in normal-looking urothelium and suggests that random biopsies add very little prognostic information (if any) to the risk of recurrence, but they do add prognostic information to the risk of progression.

The major hypothesis for the prognostic relevance of dysplastic changes in mucosal biopsies is that these changes reflect a premalignant state of the entire urinary bladder surface. New tumor occurrences originate from these intraurothelial lesions.[34] If this hypothesis is true, why then (at least in our study) did the random biopsies have very little predictive value regarding the risk of recurrence? One possible reason is the very high frequency of recurrences in superficial bladder cancer which may obscure a relatively small extra risk because of intraurothelial abnormalities. Another possible explanation for the absence of a prognostic effect on the risk of recurrence relates to the interpretation of random urothelium biopsies. Considerable variability exists in the assessment of the presence and classification of flat, dysplastic lesions and the separation of these presumably premalignant changes from reactive changes.[35] In a recent study by the British Medical Research Council, six expert pathologists examined 92 representative random biopsy slides. The reproducibility of interpretation appeared to be so poor that the authors questioned random biopsies as a useful guide for defining therapy.[36] For example, one pathologist found mild or moderate dysplasia in 60% and severe dysplasia or CIS in 27% of the slides compared to another pathologist who found dysplasia in 6% and CIS in a further 7%. Pathologists replicated their first assessment on only 62% of occasions, although most of the disagreement was by only one grade.[36]

The reproducibility of interpretation improves with the severity of the lesions. Therefore, one could argue that only CIS rather than dysplasia and CIS should be regarded as an abnormality in order to increase the prognostic significance. We examined this in our study but found that the hazard ratio for the risk of first recurrence increased only slightly from 1.12 to 1.17 (not statistically significant).

Despite the current lack of reproducibility in the interpretation of random biopsies, the presence of dysplasia and/or CIS in apparently normal urothelium appears to have prognostic value regarding future tumor progression. Adjusted for the effect of other prognostic indicators, concomitant dysplasia or CIS increased the risk of progression with 80%. This increase in risk of progression, however, does not necessarily mean that it is worthwhile to use random biopsies as an additional guide in the choice of treatment for primary superficial bladder cancer. This also depends, for instance, on the efficacy of adjuvant intravesical chemotherapy or BCG for preventing tumor progression. This efficacy is believed to be rather poor,[37,38] which is in accordance with the absence of any effect of adjuvant therapy in our study (although this finding is difficult to interpret in a non-randomized study). Furthermore, the usefulness of random biopsies depends on the number of patients who will be treated adjuvantly because of concomitant dysplastic abnormalities. Because of the correlation with other prognostic factors, such abnormalities are relatively rare findings in patients who are routinely treated with TUR alone. Therefore, a medical decision analysis is needed to study the clinical relevance of taking random urothelium biopsies on a routine basis.

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CHAPTER 7

PREDICTABILITY OF RECURRENT AND PROGRESSIVE DISEASE IN INDIVIDUAL PATIENTS WITH PRIMARY SUPERFICIAL BLADDER CANCER

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SUMMARY

The ultimate goal of prognostic assessment is optimization of individual counselling. Very often, however, studies on prognostic factors focus on discriminating between high risk and low risk subgroups without considering the relevance of one or more factors for predicting disease outcome in individual patients. This ability to predict disease outcome on a patient level may turn out to be poor despite the existence of highly statistically significant prognostic factors. As an example, we quantified the accuracy of prediction of future recurrences and disease progression in individual patients with superficial bladder cancer.

The study cohort consisted of 1674 patients with primary superficial bladder cancer who were followed prospectively between 1983 and 1991 in the Netherlands. In each patient, tumor stage, grade, extent and multicentricity were assessed. Biopsies of cystoscopically normal-looking urothelium were taken from 1001 patients. By analyzing one-half of the patients with proportional hazards regression, we computed relative risks of recurrence and progression. A prognostic index score based on these relative risks was then applied to the other half of the patients to determine whether group outcome could be predicted accurately. To assess the accuracy of prediction in individuals we used a method similar to the construction of ROC curves in diagnostic test assessment.

The 3-year risk of first recurrence was 55% (95% CI: 51%-59%). The 3-year risk of first progressive disease was 10% (95% CI: 8%-12%). For the risk of first recurrence, tumor stage, tumor extent and multicentricity were found to have statistically significant prognostic ability. Prognostic factors for the risk of disease progression were tumor stage, grade, multicentricity and the result of urothelium biopsies. For patients with a prognostic index score which suggested a low risk for recurrent and progressive disease, the predicted 3-year risk of first recurrence was still 44%, but the predicted 3-year risk of progression was only 3%. For patients with a prognostic index score which suggested a high risk, the predicted risks were 74% and 22%, respectively. These predicted risks appeared to be fairly accurate when applied to the other half of our case series. However, in any two patients chosen at random, the chance that the patient with the worst predicted prognosis would have a shorter recurrence-free and progression-free follow-up interval, was calculated to be only 58% and 67%, respectively.

Although the available prognostic factors in superficial bladder cancer may be useful for identifying high risk and low risk subgroups, predictability in individuals is highly inaccurate. More relevant prognostic factors are needed to reduce current overtreatment and undertreatment and to improve the follow-up policy. Future prognostic research should place more emphasis on prediction in individuals.

INTRODUCTION

The ultimate challenge of prognostication in clinical practice is accurate prediction of the clinical course in individual patients.[1] Very often, research into prognostic factors has dealt with the identification of high risk and low risk subgroups of patients by assessing the statistical significance of one or more host or disease characteristics. Occasionally, the accuracy of identification of these subgroups has been quantified. Prognostic assessment studies, however, have rarely emphasized the ability to predict disease outcome in individuals. This predictive ability in individuals may be very disappointing despite the existence of a number of statistically significant prognostic factors. We aimed to illustrate this with an example in superficial bladder cancer.

In 1991, bladder cancer, excluding carcinoma in situ, was estimated to contribute 50,200 new cases of cancer in the United States.[2] Among newly diagnosed cases, approximately 65% initially present with superficial transitional cell carcinomas, not invading the muscle layer of the bladder. In more than half of these patients, tumors recur after primary treatment with transurethral resection. 10%-20% of these patients develop muscle-invasion or metastatic disease.[3] To prevent or delay tumor recurrence and (possibly) muscle-invasion, adjuvant intravesical instillations with chemotherapeutical or immunotherapeutical agents can be applied.

In order to optimize treatment policy, much research has been conducted into the identification of prognostic factors for the risk of recurrence and progression. For these two types of disease outcome, the most important factors appear to be clinical and histo-pathological characteristics, such as tumor stage, grade, multicentricity, size and (possibly) the presence of dysplastic abnormalities in cystoscopically normal-looking urothelium.[4-9] Several other host and tumor characteristics have been explored for their prognostic ability, e.g., blood group antigen expression, DNA ploidy, certain biochemical factors and tumor associated antigens.[10] Until now, these characteristics have not been used routinely in urological practice, mainly because there is still no agreement on their (independent) prognostic relevance.

In the present study, we prospectively analyzed the clinical course of patients with superficial bladder cancer in an attempt to predict future tumor recurrences and disease progression. Prognostic index scores were constructed to determine the accuracy of disease outcome predictions not only for groups of patients, but also for individuals.

METHODS

The study cohort

Between January 1983 and January 1990, the Dutch South-East Cooperative Urological Group prospectively documented the patient and tumor

characteristics of 2705 cases with primary bladder cancer. Of these, 1745 (64.5%) had histologically verified superficial transitional cell carcinoma (TCC). Superficial was defined as tumor extension limited to the mucosa (TNM stage pTa) or the lamina propria (pT1) of the bladder wall with or without concomitant carcinoma in situ in random biopsies of normal-looking urothelium. Patients with primary carcinoma in situ (pTis: N=52) were not included in the study cohort because pTis was considered to be different from pTa and pT1 tumors owing to its relatively aggressive behavior. Muscle tissue from the depth of the transurethral resection (TUR) of the bladder tumor was required to ascertain the tumor stage. The following items were registered from each patient: date of birth, gender, date of histological diagnosis, grade of differentiation (according to the WHO grading system,[11] TNM classification (UICC, 1978), multicentricity, tumor extent and the result of random biopsies from normal-looking urothelium at the time of primary surgery. All the patients were treated with TUR. The necessity to apply adjuvant treatment was judged by the urologist. The patients were followed-up every three months. At every visit, cystoscopy and urine cytology were performed to detect recurrences. The median follow-up for the study cohort was 3.5 years. In 1991, all the data from the project were reviewed using the medical files.

Of the 1745 patients with superficial TCC, 1116 were treated with TUR alone and 558 were treated with adjuvant intravesical instillations (Adriamycin, Mitomycin-C, or Bacillus Calmette-Guérin vaccine). The remaining 71 patients were treated with interstitial radiotherapy (N=17), external radiotherapy (N=33) and cystectomy (N=21). These 71 patients were excluded from the analyses. Baseline characteristics of the study population (N=1674) are listed in Table 7.1.

Analysis of prognostic factors

As disease outcomes, a first recurrence and first evidence of progressive disease were considered. We defined progressive disease as a shift to a higher disease stage category or the development of regional or distant metastases. The follow-up of patients without any recurrence and disease progression was censored to the date of the last hospital visit. In case of death not related to the bladder cancer, the follow-up was censored to the date of death. Cox's proportional hazards model for censored follow-up data was used to identify prognostic factors for recurrence and progression.[12] In the model development, the following factors were evaluated multivariately for their statistical significance, using the likelihood ratio test with a significance level of P=0.10: age, gender, tumor stage (pT1 versus pTa), tumor grade (grade 3 versus 2 versus 1), multicentricity (multiple versus solitary), therapy (adjuvant intravesical instillations with chemotherapy or BCG versus TUR alone), tumor extent, the result of random bladder biopsies and interactions between therapy and any of the other factors. In the analyses, we did not specify the drug used for intravesical instillations. Although there is some evidence that the response rates to BCG are somewhat higher, differences in the efficacy of

TABLE 7.1 *Characteristics at disease presentation of 1674 patients with primary superficial TCC of the bladder*

	N	%
Gender		
Male	1351	80.7
Female	323	19 3
Age		
≤ 39	46	2.7
40-49	99	5.9
50-59	278	16.6
60-69	525	31.4
70-79	526	31.4
80+	200	11.9
Stage		
pTa	1179	70.4
pT1	495	29.6
Grade[#]		
1	668	39.9
2	772	46.1
3	234	14.0
Multicentricity		
Solitary	1181	71.0
Multiple	483	29.0
Unknown	10	
Areas involved		
Neck only	26	1.6
Trigone only	52	3.1
Posterior wall only	120	7.2
Right lateral wall only	373	22.3
Left lateral wall only	386	23.1
Dome only	34	2.0
Anterior wall only	24	1.4
2 Areas	357	21.3
3 Areas	156	9.3
≥ 4 Areas	146	8.7
Quadrant biopsies (N=1001)[@]		
No abnormalities	793	79.3
Dysplasia	137	13.7
Carcinoma in situ	71	7.1

[#] *In cases with different grades in one tumour, the highest grade was documented*
[@] *Quadrant biopsies were not taken from 673 patients*

chemotherapeutical agents are known to be small.[13-15] Tumor extent was defined as the number of bladder areas involved (3 or more versus 2 versus 1) instead of the size of the tumor. We distinguished the following bladder areas: bladder neck, trigone, dome, anterior and posterior wall, and left and right lateral wall. Although the urologists who participated in the project were asked to take four random biopsies in macroscopically normal-looking urothelium (left and right lateral wall, trigone and dome), this was not done in 673 out of the 1674 patients. It appeared that some of the urologists took biopsies from all of their patients, irrespective of the patient or tumor characteristics, while others never did. As expected, therefore, the prognostic profile of the patients (as listed in Table 7.1) in the biopsied group and in the not biopsied group was the same. In order to make the series as large as possible, the group with no biopsy result was considered to be a separate biopsy category, in addition to the categories dysplasia or CIS, and normal. For assessment of dysplasia pathologists used the following grading system: absent, mild, moderate, severe, CIS. According to this system, CIS is a grade 3 lesion by definition. All non-dysplastic changes, such as hyperplasia, were categorized as 'normal'.

Split-sample

Preferably, the extent to which one is able to predict disease outcome with one or more prognostic factors should be evaluated in a patient series that was not used to identify these prognostic factors. To allow assessment of this predictive ability in "another" patient series, the data set was split at random into a "*training*" or model development sample, and a "*test*" or model validation sample. Only the *training* sample was used for prognostic factor analyses. The *test* sample was used to evaluate whether predictions from the model could be replicated on other patient samples or whether the model was "tailor-made" to fit all variability in the *training* sample.[16]

Prognostic index and its reliability

The results of the prognostic factor analyses on the *training* sample were used to construct a prognostic index score for recurrent disease (PI^R) and for progressive disease (PI^P). Both scores were calculated for each patient by summing the regression coefficients (beta values) of the final Cox models on recurrence and progression. Regression coefficients were considered for inclusion in the PI scores if at least one of the categories of the tumor characteristic was statistically significant. A high score indicated that a patient had a poor prognostic profile.

The value of a prognostic index in clinical practice depends on its predictive accuracy, which has two major components: reliability and discrimination. Reliability refers to the amount of agreement between the predicted and observed clinical course of disease. For instance, if patients with a certain prognostic profile are predicted to have a 3-year risk of 50% of recurrent disease, then 50% of such patients should have a recurrence within 3 years. We compared the observed and predicted risks of recurrence and progression

in three subgroups of patients (a low, intermediate and high risk group) in the *test* sample. We first calculated the predicted risks for each patient separately using the proportional hazards assumption:[12,17]

$S_i(y) = S_r(y)^{EXP(\delta PI)}$ where

$S_i(y)$ = the predicted probability of still being disease-free y years after initial treatment for individual i in the *test* sample

$S_r(y)$ = the observed fraction of patients with the best prognostic profile in the *training* sample (the reference group) who were disease-free after y years

δPI = the prognostic index score for individual i in the *test* sample minus the mean prognostic index score of the aforementioned reference group.

Finally, these individual probabilities of being disease-free were averaged for the three subgroups. The definition of these three "risk" groups was based on the distribution of the prognostic index scores, so that the low and high risk group each represented at least 20% of all the patients.

Prognostic index and its discrimination ability

The second component of predictive accuracy, discrimination, refers to the ability to distinguish between individual patients who will have a positive disease outcome and those who will have a negative disease outcome. This predictive discrimination can be quantified through a method proposed by Harrell and associates, in which every possible pair of patients in the study is compared with respect to the observed and predicted outcome.[18-19] The resulting index "**c**" (for "**concordance**") is the probability that in a pair of patients chosen at random, the predicted and observed outcomes are concordant, i.e., the patient with the worst predicted prognosis (the higher PI) will indeed have a shorter disease-free follow-up interval, and vice versa. **C** values in the region of 50% indicate that the clinical value of a prognostic index to determine which patient has a better prognosis, is as good as the flip of a coin. Values of **c** near 100% indicate perfect prediction of disease outcome. In fact, this method to ascertain the ability to discriminate patients on their course of disease is analogous with the construction of Receiver Operating Characteristic (ROC) curves used in diagnosis.[20] The interpretation of **c** is analogous with the interpretation of the area under a ROC curve.

We calculated **c** by comparing the prognostic index score and the observed clinical course in all possible pairs of patients in both the *training* sample and the *test* sample.

RESULTS

The 3-year actuarial risk of first recurrence in the *training* sample (N=854) was 55% (95% CI: 51%-59%). The 3-year risk of first progressive disease was 10% (95% CI: 8%-12%). From proportional hazards regression, tumor stage, extent and multicentricity appeared to have predictive ability for the risk of first recurrence. Age, gender, tumor grade and random biopsies had no (statistically significant) additional value for prediction. Adjuvant intravesical chemotherapy or immunotherapy instillations seemed to lower the risk of first recurrence, but had no statistically significant independent effect on the risk of progression. For this risk of progression, the most important prognostic factors were tumor stage, grade, multicentricity and dysplasia or CIS in random biopsy specimens. In both the recurrence and progression model, there were no significant interactions between therapy and the other factors. The final models with regression coefficients (beta), standard errors and P values based on the *training* sample are shown in Table 7.2. The risk of first recurrence as well as the risk of progressive disease hardly increased after 3 years of follow-up. Therefore, we evaluated whether the results of the prognostic factor analysis would change with restriction of the follow-up period to a maximum of 3 years. This restriction appeared to have no effect on the results presented in Table 7.2.

By summing the beta coefficients, a prognostic index score for progression (PI^P) was calculated for each patient in the *test* sample (N=820). For instance: for a patient with multiple pT1G2 tumors and dysplasia or CIS in the biopsy specimens, $PI^P = 0.56 + 0.53 + 0.95 + 0.64 = 2.68$. PI^P for a patient with a solitary pTaG1 tumor without any abnormalities in the biopsy specimens was 0. Subsequently, all the patients were categorized in a low, intermediate, or high risk group according to their PI^P (Table 7.3).

Likewise, a PI^R was calculated for each patient in the *test* sample, but now only for the patients who had not received adjuvant intravesical instillations (N=554). We used this restriction because we did not want to include therapy (an intervention factor instead of a host or tumor characteristic) in a prognostic score.

In order to evaluate the reliability of PI^R and PI^P we compared the observed and predicted actuarial risks of tumor recurrence and progression in the *test* sample (Figures 7.1 and 7.2; Note that the scales of the Y axis in the figures differ). Both the risks of recurrence and the risks of progression were fairly close to the predicted risks, even though the risk of recurrence was somewhat underestimated in the high risk group and overestimated in the low risk group.

The risk of progression was slightly underestimated in the intermediate risk group. Nevertheless, the reliability of the indices seemed to be quite good. For example, if we predict that the 4-year risk of progression for a group of patients with a solitary pTa grade 1 or 2 tumor without any abnormalities in the random biopsies is 3%, we can be quite sure that in approximately 3% of these patients progression will be diagnosed within 4 years (Table 7.3).

This high reliability of both PI^R and PI^P does not necessarily mean that we will be able to predict the disease outcome in individual patients. To examine this, we compared all possible pairs of patients in the *test* sample (the number of pairs was 335,790) and calculated the **c** score of predictive discrimination

TABLE 7.2 *Final model results of the Cox regression analysis in 854 patients with superficial TCC of the bladder (the "training" sample)*

Prognostic Factor	Recurrence model			Progression model		
	Beta	SE	P	Beta	SE	P
Tumor stage						
pTa	0			0		
pT1	0 40	0 10	<0 001	0 56	0 23	0 02
Tumor grade						
1	-			0		
2	-			0 53	0 30	0 07
3	-			0 98	0 35	0 005
Multicentricity						
Solitary	0			0		
Multiple	0 27	0 12	0 03	0 95	0 22	<0 001
Number of areas involved						
1	0			-		
2	0 17	0 13	0 18	-		
3 or more	0 52	0 14	<0 001	-		
Therapy						
TUR alone	0			-		
Instillations	-0 43	0 11	<0 001	-		
Result of random biopsies						
Normal	-			0		
Not performed	-			0 37	0 25	0 15
Dysplasia/CIS	-			0 64	0 29	0 03

Note: Tumor grade and random biopsy result had no statistically significant effect in the recurrence model; likewise, number of areas involved and therapy were not significant in the progression model

The **c** for recurrent disease was only 57.6%. The **c** for progressive disease was 67.3%. (In the *training* sample these percentages were 58.2% and 71.9%, respectively.) Thus, in two patients chosen at random, the chance that the patient with the worst predicted prognosis will have a shorter recurrence-free

follow-up interval was no more than 58%, even in the sample used for model development. This prediction, therefore, is not much better than a guess. The individual discrimination ability for progression was only slightly higher. If we compare all the possible pairs of patients with respect to the progression-free interval, then in approximately 67% of these comparisons the patient with the better prognosis will stay progression-free for a longer period of time.

TABLE 7.3 *Observed and predicted actuarial risks of first recurrence and progressive disease in the "test" sample (N=820)[$] according to PI^R and PI^P "risk groups"*

		Observed (+ predicted) risk of first recurrence (expressed as percentages)			
Risk group (% of all patients)	PI^R range[#]	1 year	2 year	3 year	4 year
Low (40%)	0	21 (24)	32 (37)	38 (44)	42 (48)
Intermediate (40%)	0.17-0.57	40 (32)	56 (49)	60 (57)	63 (61)
High (40%)	0.67-1.19	60 (48)	71 (66)	81 (74)	84 (78)
		Observed (+ predicted) risk of first progression (expressed as percentages)			
Risk group (% of all patients)	PI^P range[#]	1 year	2 year	3 year	4 year
Low (36%)	0-0.53	2 (2)	3 (2)	4 (3)	4 (3)
Intermediate (42%)	0.56-1.73	4 (4)	9 (5)	10 (6)	12 (8)
High (22%)	1.85-3.13	9 (11)	13 (16)	18 (18)	21 (22)

[$] *For PI^R the "test" sample consisted of 554 patients treated with TUR only*
[#] *PI^R and PI^P are not continuous variables*

DISCUSSION

In urological practice it is known that the clinical course of superficial bladder cancer is rather unpredictable, despite an ongoing search for new prognostic factors. In many cases, the significance of prognostic factors has been claimed on the grounds of a small P value. This statistical significance, however, reflects the likelihood that a given difference in disease outcome could have

FIGURE 7 1 *Observed and predicted risk of first recurrence in 554 patients with superficial TCC treated with TUR alone (the "test" sample) according to three prognostic index (PI^R) "risk groups"*

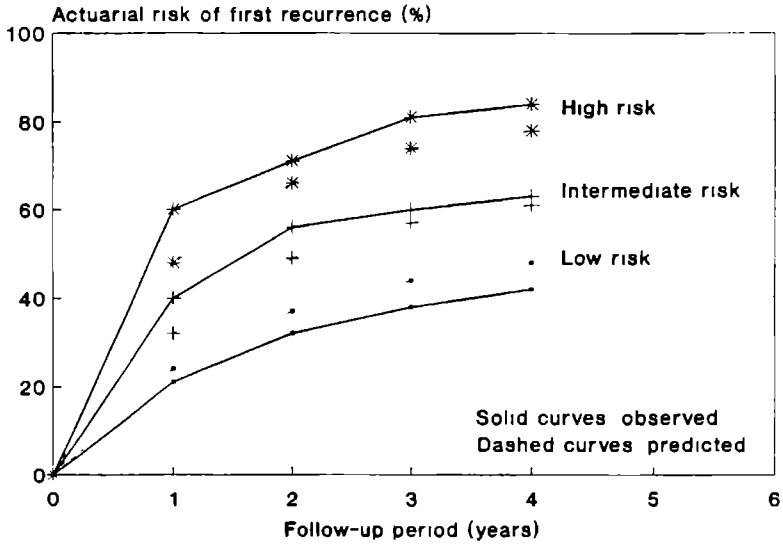
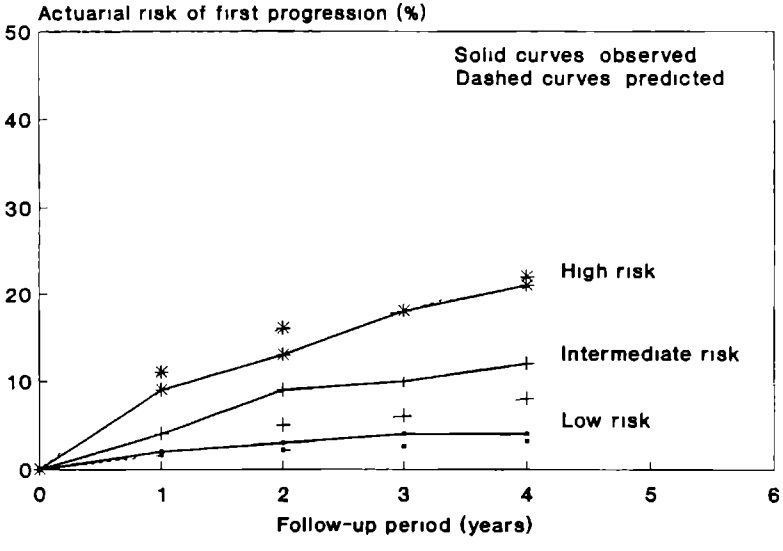


FIGURE 7 2 *Observed and predicted risk of first evidence of progressive disease in 820 patients with superficial TCC (the test sample) according to three prognostic index (PI^P) "risk groups"*



arisen by chance; it does not measure the extent to which the factor can differentiate low risk from high risk subgroups of patients. Even if a prognostic factor does have such ability to differentiate subgroups, this is no guarantee that prediction of disease outcome for individual patients (the ultimate goal of prognostic factors) will be accurate. This predictive accuracy can be studied with the aid of a prognostic index.

In this paper, prognostic indices are presented for the risk of first recurrence and for the risk of progressive disease in primary superficial bladder cancer. The former index was based on tumor stage, multicentricity and the number of bladder areas involved. The latter was based on tumor stage, grade, multicentricity and the result of random biopsies. Although adjuvant intravesical therapy also had a statistically significant (beneficial) effect on the risk of recurrence, we did not include therapy in the prognostic index and applied the index to patients treated with TUR alone. The prognostic index for progression applies to all the patients because intravesical therapy did not lower the risk of progression. This supports the hypothesis that intravesical therapy does not alter the ultimate outcome of the disease,[21-22] but the finding has to be interpreted with some caution because our study was not initiated to study therapy effects. Furthermore, some evidence exists that especially BCG may prevent disease progression in high-risk patients.[23]

It is shown that the prognostic indices can be used to differentiate subgroups of patients with different risks for disease outcome. By summing the prognostic-factor-specific model coefficients in Table 7.2 one can easily see which risk group a new patient belongs to. As is shown in Table 7.3 and Figures 7.1 and 7.2, where the observed risks of recurrence and progression in a *test* sample are compared to the corresponding predicted risks, the prognostic indices are fairly reliable. Although for the intermediate risk group, the observed and predicted risks of progression seem to differ considerably, the maximum absolute difference is only 4%. Despite this satisfactory reliability of the prognostic indices however, especially the index for recurrent disease does not have sufficient predictive accuracy for individuals. This is not very surprising considering the urological experience that many patients with a (relatively benign) solitary small tumor confined to the mucosa develop recurrences (in our study approximately 40% within 3 years!), whereas most patients with (presumed aggressive) multiple pT1G3 tumors do not develop progressive disease (approximately 75%). Even though, this poor individual predictability has not been quantified before. It was shown that prediction of recurrence-free survival ("c" = 58%) was only slightly better than a guess based on the flip of a coin. Prediction of progression-free survival ("c" = 67%) was relatively good but still far from perfect. This means that in superficial bladder cancer individual counselling based on a patient's prognostic profile is hardly possible.

If we cannot use a prognostic index for individual counselling, then what is the value of such an index? First, it can be used to select a subgroup of patients with a low risk of progression so that they can be scheduled for

longer intervals between successive endoscopies, thus reducing hospital visits and financial cost. According to our study, this subgroup consists of patients with a solitary pTa grade 1 or grade 2 tumor without any concomitant mucosal abnormalities. Even in this group (with a predicted 3-year risk of progression of only 3%) recurrences are very common, but these recurrences can be easily managed by repeated resections or fulguration and, therefore, do not require any additional measures.[24] However, if we modify the follow-up schedule we are making an important assumption, i.e. that the delay of resection or fulguration of recurrences will not increase the risk of progression in this subgroup.

Second, prognostic index scores can be used in future studies on new prognostic tests. In such studies it might be worthwhile to start with the construction of a prognostic index based on the factors already available. Subsequently, a prognostic index can be made wich includes the new test. This would enable the evaluation of the test to be based on any improvement in the predictive accuracy of the index, instead of basing the evaluation on statistical significance only.[19]

Our results so far show that a prognostic index is not very useful in the planning of treatment for superficial bladder cancer. The insufficient predictive accuracy of such an index inevitably leads to considerable overtreatment and undertreatment. This predictive accuracy may improve with more objective criteria for the assessment of the prognostic factors already available. Especially the reproducibility of tumor grade and concomitant dysplastic changes in normal-looking urothelium is known to be poor,[8,25,26] but it is also possible for pathologists to make different interpretations of the tumor stage category.[9,27-29] In our study, most resection specimens were not reviewed by a reference pathologist. This may have had some effect on our results. Even though, we aimed to evaluate the predictability of disease outcome in a case series which is representative for all patients with superficial bladder cancer. Because review pathology is no routine practice, it could have hampered generalizations of our results. Review pathology, of course, is no solution for poor predictability of recurrence and tumor progression in every day clinical practice. More objective criteria for prognostic factors may be a solution. However, in addition to obtaining more objective criteria for prognostic factors, an ongoing search for new (and stronger) prognostic factors is probably necessary.

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CHAPTER 8

SHOULD RANDOM UROTHELIUM BIOPSIES BE TAKEN FROM PATIENTS WITH PRIMARY SUPERFICIAL BLADDER CANCER? A DECISION ANALYSIS

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SUMMARY

The presence of concomitant dysplasia or carcinoma in situ in normal-looking urothelium is considered to be of prognostic value in patients with superficial transitional cell carcinoma of the bladder. Therefore, random urothelium biopsies may be a useful additional guide for defining therapy in order to prevent or delay tumour recurrence. The purpose of this study was to evaluate whether it is worthwhile to implement routine random biopsies in the management of patients with primary superficial bladder cancer. For this purpose, we defined and compared two hypothetical management policies, one of which incorporates random biopsies as an additional prognostic test. In the 'no-biopsy policy', all patients are treated with transurethral resection alone, except for patients with a pT1G3 tumour who are treated adjuvantly with prophylactic intravesical therapy. In the 'biopsy policy', the choice of treatment is influenced by the presence or absence of dysplastic urothelium in random biopsy specimens, again except in patients with a pT1G3 tumour who are treated adjuvantly, irrespective of the result of random biopsies.

Decision analysis was used to compare the outcome of these two hypothetical policies with respect to the expected 3-year risks of recurrence and progression. Baseline data used in the analysis originated from a large unselected case series, prospectively documented in the Netherlands. The 'biopsy policy' resulted in a 3-year risk of recurrence and a 3-year risk of progression of 52% and 11%, respectively. These 3-year risks were almost identical to the 'no-biopsy policy': 54% and 11%, respectively.

By means of a so-called sensitivity analysis we examined what the results would have been if dysplastic urothelium had been detected more often, if such dysplastic urothelium had higher prognostic value, and if intravesical therapy was more efficacious. Under very optimistic assumptions about these three characteristics, the expected 3-year risks of recurrence and progression in the 'no-biopsy policy' were 63% and 15%, respectively. With routine random biopsies, these risks were estimated to be 58% and 11%, respectively. In that case, however, intravesical therapy would have to be applied to 43% of all the patients, vs. 12% in the 'no-biopsy policy'.

In view of the expected small difference in disease outcome between the two management policies, even under fairly optimal conditions, it is our opinion that taking random biopsies of normal-looking urothelium at the time of the transurethral resection has no practical value.

INTRODUCTION

Predominant factors used to predict disease outcome in newly diagnosed patients with superficial transitional cell carcinoma (TCC) of the bladder are

tumour stage, degree of differentiation of the tumour, multicentricity and tumour size.[6-7,13-14,21,26,30,35,42,49,53] Despite these well-known prognostic factors, however, the clinical course of patients with superficial TCC appears to be rather unpredictable. It has been recognised for some time that random urothelium biopsies may improve this predictive ability. After the first paper by Eisenberg and associates in 1960,[9] numerous investigators confirmed the hypothesised prognostic relevance of concomitant dysplastic abnormalities in normal-looking urothelium.[1,6,8,12,14,34,38,43,46,50,55,57] Because of this prognostic ability it would seem reasonable to use random biopsies as an additional guide for defining therapy, i.e., adjuvant intravesical instillations can be administered in the case of pathological findings, while transurethral resection (TUR) alone can be applied otherwise. However, the ultimate benefit of random urothelium biopsies as an additional prognostic test is not determined solely by its prognostic ability. The rationale of taking random urothelium biopsies from patients with primary superficial bladder cancer depends on several factors:

- the number of patients who have dysplastic abnormalities in normal-looking urothelium;
- the accuracy and reproducibility of the assessment of dysplastic abnormalities in biopsy specimens;
- the biological association between dysplastic changes and future new tumour occurrences ('recurrent tumours') and tumour progression;
- the correlation between dysplastic abnormalities and other prognostic factors;
- the number of patients who would have been treated with intravesical instillations anyway;
- the efficacy of intravesical therapy for preventing tumour recurrences and progressive disease.

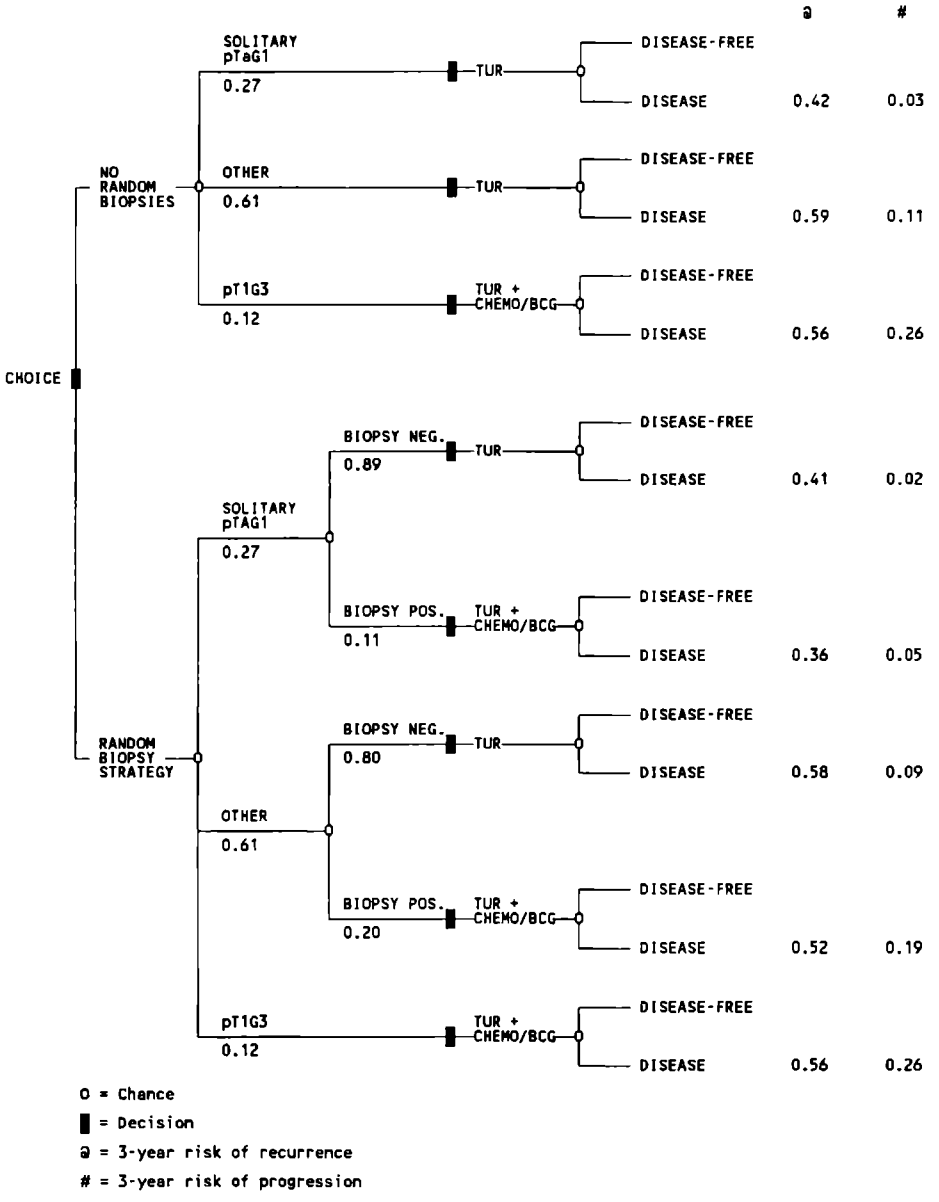
In this study, we evaluated the benefit of using random biopsies as an additional prognostic test in primary superficial bladder cancer. By using decision-analytical methods, it was attempted to take all the aforementioned factors into account. Quantitative data needed for the analysis were derived from a large case series documented prospectively in the Netherlands.

PATIENTS AND METHODS

Decision model

To evaluate the rationale of using random biopsies in the management of primary superficial bladder cancer we compared two hypothetical policies. See Figure 8.1. Both policies deal with an unselected population of patients with suspected primary superficial TCC, but only one incorporates random biopsies in its management. In all the patients at least one papillary tumour is seen at cystoscopy, without any concomitant macroscopically visible lesions suspicious of carcinoma in situ (CIS). Because the prevalence of CIS in mucosa with a

FIGURE 8.1 *Decision tree for the management of primary superficial TCC of the bladder (applies only to patients with bladder mucosa not suspicious of CIS)*



O = Chance

▮ = Decision

@ = 3-year risk of recurrence

\# = 3-year risk of progression

red and flat or mossy appearance is very high,[52] these lesions have to be biopsied anyway.[44]

In our first hypothetical management policy, no random urothelium biopsies will be taken. The choice of treatment is based on the histopathology of the resected tumour(s): all patients are treated with TUR only, except for the patients with a pT1G3 tumour. In the alternative policy, random urothelium biopsies will be taken from all the patients at the time of TUR. We assume that these random biopsies are primarily taken to optimise treatment management. If the histopathology reveals dysplasia or CIS in at least one biopsy specimen, then the patient will be treated adjuvantly, otherwise the treatment will be TUR alone. An exception is made for the patients with a pT1G3 tumour who will be treated with adjuvant intravesical therapy irrespective of whether or not dysplastic abnormalities are diagnosed in normal-looking mucosa.

Patients

All the quantitative data needed for the decision-tree evaluation were derived from a large unselected series of newly diagnosed bladder cancer patients prospectively documented by the Dutch South-East Cooperative Urological Group. This case series is described in detail elsewhere.[54,60] In summary, the series consisted of 1,745 patients with histologically verified primary superficial TCC diagnosed between January 1983 and December 1989. Superficial was defined as tumour extension limited to the mucosa (TNM stage pTa) or the lamina propria (pT1) of the bladder wall with or without concomitant abnormalities in random biopsies of normal-looking urothelium. Patients with primary carcinoma in situ (pTis: N=52) were not included in the study cohort. Owing to its relatively aggressive behaviour, primary CIS was considered to be a separate entity. Of all 1,745 patients, 1,116 were treated with TUR alone, 558 had TUR plus intravesical instillations (Adriamycin, Mitomycin C, or Bacillus Calmette-Guérin) and 71 received additional treatment with interstitial or external radiotherapy or cystectomy.

Twenty-seven per cent of all the patients presented with a solitary pTaG1 tumour (see Figure 8.1). Twelve per cent had a solitary or multiple pT1G3 tumour. The remaining 61% had superficial tumours other than solitary pTaG1 and pT1G3.

Although the urologists who participated in the project were asked to take four cold-cup biopsies (left and right lateral wall, trigone and dome) of normal-looking urothelium from all of their patients during initial TUR, this was not done in 701 patients. It appeared that some of the urologists took biopsies from all of their patients, irrespective of the patient or tumour characteristics, while others never did. Therefore, the prognostic profile of the patients in the biopsied group and in the not-biopsied group was the same (Table 8.1).

TABLE 8.1 *Clinical characteristics at disease presentation in 1,745 patients with primary superficial TCC*

Factor	Cases biopsied (N=1,044)		Cases not biopsied (N=701)	
	N	%	N	%
Age				
0-49	92	8 8	57	8 1
50-59	189	18 1	106	15 1
60-69	333	31 9	217	31 0
70-79	318	30 5	228	32 5
80+	112	10 7	93	13 3
Sex				
Men	857	82 1	558	79 6
Women	187	17 9	143	20 4
Tumour stage				
pTa	693	66 4	494	70 5
pT1	351	33 6	207	29 5
Tumour grade #				
1	371	35 5	298	42 5
2	465	44 5	328	46 8
3	208	19 9	75	10 7
No of areas involved $				
1 area	633	60 6	409	58 3
2 areas	233	22 3	140	20 0
3 or more	178	17 0	152	21 7
Multicentricity				
Solitary	751	72 4	472	67 8
Multiple	286	27 6	224	32 2
Unknown	7		5	
Biopsy result				
No abnormalities	816	78 2	-	
Dysplasia	142	13 6	-	
Carcinoma in situ	86	8 2	-	

 # In cases with various grades in one tumour, the highest grade was documented
$ Instead of the size of the tumour, the number of bladder areas in which tumour tissue was found was documented

The results of random biopsies were classified positive if dysplasia (either mild, moderate or severe) or CIS was found in one or more specimens. Of all the patients who were biopsied (N=1,044), 22% had abnormalities in at least

one biopsy specimen (14% dysplasia and 8% CIS). The presence of these concomitant abnormalities was strongly correlated with the histopathology of the primary tumour. Dysplasia or CIS was detected in 11% of the solitary pTaG1 patients, in 49% of pT1G3 patients and in 20% of all the remaining patients with other tumours.

All the patients were followed-up every three months with cystoscopy and urine cytology. Follow-up data were documented until July 1991. In 1991, all the patient and disease characteristics at first presentation as well as the follow-up data were reviewed using the medical files. The follow-up of patients without any recurrence and disease progression was censored to the date of the last hospital visit. In case of death not related to the bladder cancer, the follow-up was censored to the date of death. The median follow-up period of the study cohort was 3.5 years.

Analysis

The two hypothetical policies (Figure 8.1) were compared with regard to the expected 3-year risk of recurrence and the expected 3-year risk of progression (progression was defined as a shift to a higher tumour stage category or the development of regional or distant metastases). For this, we calculated the 3-year risks of recurrence and progression for each branch of the decision tree in Figure 8.1 using the Cox's proportional hazards model.[5]

The proportional hazards model was used for the following reason. Because the prognostic ability of concomitant dysplastic changes in normal-looking urothelium and the beneficial effect of adjuvant intravesical therapy are very important for the conclusions from our study we intended to perform a so-called sensitivity analysis. In order to enable a sensitivity analysis (*i.e.* an evaluation of the stability of a conclusion from a decision analysis by varying the quantitative value of one or more characteristics in a decision tree) we modelled the time to recurrence and time to progression as a function of tumour characteristics, the result of random biopsies and the applied therapy. The resulting hazard ratios (or relative risks) from the model reflect the prognostic ability of these factors.

The factors which were fixed in the Cox model were the type of tumour (solitary pTaG1 vs. pT1G3 vs. other), random biopsy 'result' (not performed vs. normal mucosa vs. dysplastic mucosa) and therapy (TUR alone vs. adjuvant intravesical chemotherapy or BCG; patients who were treated more aggressively (N=71) were excluded from the analysis). Possible (additional) interactions between these factors were tested for their statistical significance with a step-wised model using the likelihood ratio test with significance level P=0.10. None of the interaction factors appeared to be statistically significant. The underlying proportionality assumptions of the Cox model with the fixed factors appeared to hold and the preditive reliability of the model was found to be fairly good.[61] The results of the multivariate proportional hazards analysis are summarised in Table 8.2.

According to the definitions we used for the factors in the model, the reference group comprised the patients with a solitary pTaG1 tumour who were not biopsied and were treated with TUR alone. The 3-year actuarial risk of recurrence in this reference group was 42%; the 3-year actuarial risk of progression was 3%. With these observed risks and the relative risks in Table 8.2, the expected risks of recurrence and progression for each branch of the decision tree were calculated using the proportional hazards assumption:

$R_Y = 1-(1-R_O)^{\Pi rr}$ where:

R_Y = the expected 3-year risk of recurrence (or progression) in patients in a particular branch of the tree (Y),
R_O = the 3-year risk of recurrence (0.42) or the 3-year risk of progression (0.03) in the reference group,
Πrr = product of the branch-specific relative risks.

For example, the expected 3-year risk of recurrence in patients with a solitary pTaG1 tumour (RR=1) who have concomitant dysplastic abnormalities in normal-looking urothelium (RR=1.11) and who received intravesical instillations (RR=0.73) is:

$R_Y = 1-(1-0.42)^{(1*1.11*0.73)}$

$= 1-(0.58)^{(0.81)}$

$= 0.36$ or 36%

Subsequently, the two hypothetical management policies in the decision tree were evaluated using the computer programme DECISION MAKER.[47]

RESULTS

The 3-year risks of recurrence and progression for all the patient subgroups in the two management policies are summarised in Figure 8.1. Of all the patients with a solitary pTaG1 tumour who had been treated with TUR alone, 42% had at least one recurrence within 3 years. Only 3% manifested progressive disease. These risks were only slightly lower when random biopsies showed no mucosal abnormalities. In the patients who had such concomitant mucosal abnormalities, the risks of recurrence and progression were higher. Unlike the risk of progression, however, the higher risk of recurrence was totally compensated for by the prophylactic effect of intravesical therapy. In our study, intravesical chemotherapy or BCG was apparently less effective for preventing progression. The same phenomenon was seen in the patients with a

tumour other than solitary pTaG1 or pT1G3. When treated with TUR alone, this group of patients had risks of recurrence and progression of 59% and 11%, respectively. In the case of a normal random biopsy result, these risks were 58% and 9%, respectively Due to intravesical therapy, the risk of recurrence decreased to 52%, despite the finding of concomitant dysplastic urothelium. In this case, however, the risk of progression increased to 19%. In both management policies, the patients with a pT1G3 tumour were treated with intravesical therapy. The 3-year risks of recurrence and progression in these patients were 56% and 26%, respectively.

TABLE 8.2 *Results of Cox's multivariate regression analyses on 1674 patients with superficial TCC of the bladder (of whom 864 suffered recurrent disease and 172 progressive disease)*

Prognostic Factor	Recurrence		Progression	
	RR[#]	(95% CI)[@]	RR	(95% CI)
Tumour type				
Solitary pTaG1	1		1	
'Other'	1 65	(1 39 - 1 95)	4 52	(2 43 - 8 25)
pT1G3	2 08	(1 60 - 2 69)	9 98	(5 05 - 19 69)
Result of random biopsies				
Not performed	1		1	
No dysplastic changes	0 97	(0 84 - 1 12)	0 71	(0 50 - 1 02)
Dysplasia/CIS	1 11	(0 89 - 1 38)	1.57	(1.03 -2.39)
Therapy				
TUR alone	1		1	
Adjuvant intravesical chemotherapy/BCG	0 73	(0 63 - 0 86)	0 98	(0 70 - 1 38)

[#] *RR = Relative Risk*
[@] *95% CI = 95% Confidence Interval*

The expected overall 3-year risk of recurrence with the 'no biopsy policy', was 54%. This risk was only slightly lower if random urothelium biopsies had been taken from all the patients: 52%. This means a difference of only 2% in the risk of recurrence as the ultimate gain of taking random biopsies, whereas 27% instead of 12% of all patients would have to be treated with adjuvant intravesical therapy owing to the presence of mucosal abnormalities. Expressed in terms of a decrease in the 3-year risk of progression, no benefit

at all could be observed from taking random biopsies. In both policies, the expected 3-year risk of progression was 11%.

STABILITY OF THE CONCLUSION

The conclusion from our study should be that there is little reason to take random urothelium biopsies from patients with primary superficial TCC of the bladder. The disappointing ultimate benefit of random biopsies may be explained (at least partly) by three factors. First, the low prevalence of dysplastic changes in patients with low grade tumours (the high prevalence in patients with grade 3 tumours is clinically irrelevant because these patients are treated adjuvantly anyway); second, the poor independent prognostic ability of random biopsies; and third, the poor efficacy of intravesical chemotherapy. The latter two factors can be quantified by hazard ratios (or relative risks) which result from a multivariate proportional hazards model.[5] In our study we found that the relative risks (RRs) of the absence and presence of dysplastic changes in normal-looking urothelium were only slightly different from 1 regarding the risk of recurrence (RR=0.97 and RR=1.11, respectively) (see Table 8.2). The RRs of a negative or a positive biopsy result on the risk of progression were a little higher (RR=0.71 and 1.57, respectively). While adjuvant intravesical therapy had a protective effect on the risk of recurrence (RR=0.73), such a protective effect (adjusted for other factors) was almost absent for the risk of progression (RR=0.98).

It is possible that for some reason the prevalence of dysplasia or CIS in normal-looking mucosa was underestimated in our study. The same may also apply to the effects of random biopsies and intravesical therapy. In that case, the benefit of taking random biopsies would have been underestimated. In order to examine the stability of our conclusion, we first reviewed the literature with respect to these three factors and used the results of this review in a so-called 'sensitivity analysis'.

Literature review of key-information

With respect to the prevalence and the prognostic ability of concomitant dysplastic urothelium we reviewed 38 papers.[1-4,6,8-9,11-15,20,22-23,27-29,31,33,34,36,38-43,45-46,48,50-52,55-59] From these papers we made a selection based on the following criteria: 1) prospective (unselected) study population; 2) biopsies taken from normal-looking urothelium; 3) biopsies taken once at initial diagnosis of the primary tumour; 4) the definition of a positive biopsy result was reported; and 5) the results from the study were reported (separately) for patients with superficial disease. In the studies which fulfilled these criteria, the prevalence of dysplastic abnormalities ranged from 24% to 43% (see Table 8.3).

TABLE 8.3 *Literature review: Prevalence (%) of dysplasia or CIS in normal-looking mucosa*[@]

Reference	Study size	Prevalence in all patients	Prevalence in patients with tumour of		
			Grade 1	Grade 2	Grade 3
NBCCG-A, 1977[31]	N=61	41%			
Soloway, 1978[45]	N=42	33%	20%	30%	50%
Heney, 1978[15]	N=75	43%	15%	59%	77%
Wallace, 1979[52]	N=27	33%			
Heney, 1982[13]	N=47	38%			
Heney, 1983[14]	N=183	33%	23%	41%	55%
Smith, 1983[43]	N=112	34%			
Wolf, 1987[59]	N=259	25%	0%	17%	54%
Flamm, 1989[12]	N=216	24%	12%	24%	57%
This study	N=1044	22%	11%	20%	47%

[@] *In studies where non-dysplastic abnormalities (hyperplasia, metaplasia, inflammation, reactivity, cystitis and atypia) were used as distinct entities in addition to dysplastic changes, we considered only dysplastic changes to be positive findings*

This prevalence was strongly correlated with tumour grade. The highest reported prevalences in grade 1 and grade 2 tumours (in studies with more than 100 patients) were 23% and 41%, respectively.[14] To assess the independent prognostic ability of random biopsies regarding the risk of recurrence and the risk of progression, we tried to select studies in which adjustment was made for the effects of other prognostic factors. Such adjustment was considered to be necessary because of the strong correlation between the presence of concomitant urothelial lesions and tumour grade (but also tumour stage and multicentricity[12 59] However, all the studies which dealt with the prognostic ability of random biopsies, based their conclusions on the results of univariate analyses only Therefore, we were not able to quantify the independent prognostic effect of random biopsies from the literature.

To quantify the effect of intravesical chemotherapy and BCG on the risk of recurrence and the risk of progression we used two review papers.[16-17] In 11 randomised trials on primary or recurrent superficial TCC which compared TUR alone to Thiotepa, Doxorubicin, Mitomycin C or BCG, fairly wide discrepancies were reported between the benefits of adjuvant therapy.[16] The maximum reported decrease in the risk of recurrence was 46%, while once an increase of 5% was reported in the risk of recurrence with Thiotepa.

Combining all the study results, the 1-year risk of recurrence in patients treated with TUR alone was 44%, and the 1-year risk of recurrence in patients treated adjuvantly was 31%. Using the proportional hazards assumption (see Patients and Methods section), this protective effect of intravesical therapy can be converted into a relative risk of 0.65.

Even though there is still little evidence that adjuvant intravesical chemotherapy or immunotherapy can prevent progression to invasive bladder cancer,[25,32] a few recent studies have given some indication of a beneficial effect of BCG on progression.[10,18 19] In a review on (primary and recurrent) pT1 bladder cancer, Herr and Jakse reported progression (in tumour stage or grade) within 3-5 years in 29% of the patients treated with TUR alone. In the patients treated with intravesical chemotherapy or BCG this percentage was estimated to be 17%.[17] With these percentages, the relative risk of adjuvant intravesical therapy would be 0.55.

Sensitivity analysis

Based on the literature review, in the sensitivity analysis we assumed a prevalence of concomitant dysplasia in patients with a solitary pTaG1 tumour of 23% instead of the observed 11%. We further assumed this prevalence in patients with a tumour other than solitary pTaG1 and pT1G3 to be 41% instead of 20% as we found in our study. With these quite extreme percentages (Table 8.3), the 3-year risk of recurrence would be 55% with the no-biopsy policy and 51% with the biopsy policy. To achieve this 4% reduction in the risk of recurrence, however, an extra 31% of all the patients (43% compared to 12%) would have to be treated with intravesical therapy. Even though, the 3-year risk of progression was now expected to be 12% with both policies. This similarity of the risk of progression in both policies was caused by the poor efficacy of intravesical therapy. Therefore, in accordance with the findings from the literature we assumed the effect of intravesical therapy to be RR=0.55 instead of the RRs we estimated from our case series (0.73 for the risk of recurrence and 0.98 for the risk of progression). Furthermore, in the sensitivity analysis we assumed a fairly extreme prognostic ability of dysplastic changes in normal-looking urothelium with a RR of 3.0 (instead of 1.11 and 1.57 for the risks of recurrence and progression, respectively). With these optimistic assumptions, favouring the policy of routine random biopsies, the 3-year risk of recurrence would become 63% in the no-biopsy policy and 58% in the biopsy policy. The 3-year risk of progression, still at the expense of 43% vs. 12% of the patients treated intravesically, would be 15% and 11% in the two policies, respectively.

DISCUSSION

In our opinion the principal aim of taking random urothelium biopsies is to improve the urologist's ability to distinguish between patients who should be

treated with adjuvant intravesical therapy and those who should not. Until now, a number of authors have concluded that random biopsies may be used as a guide in defining therapy for superficial bladder cancer because they found that random biopsies have a statistically significant prognostic effect. However, several arguments exist against such a conclusion.

1. In most of the studies on the prognostic significance of biopsy results of normal-looking mucosa, the effect on the development of recurrences (or new occurrences) was studied. Because of small study sizes or short follow-up periods the effect on tumour progression was not studied, even though tumour progression is considered to be a more important characteristic of disease outcome.
2. The correlation between dysplastic changes in normal-looking urothelium and other established prognostic factors is well-known, especially the correlation with tumour grade. This means that random biopsies may not add to the prognostic information already provided by these factors. The experimental evidence of the prognostic ability of random biopsies, however, is based on studies in which no adjustment was made for the prognostic effect of other factors, e.g., through multivariate analyses.
3. The prognostic ability of random biopsies is not quantified by its degree of statistical significance. This prognostic ability (as expressed by a relative risk for instance) may be fairly poor despite a statistically significant P value. For example, for progression we found a small, but still statistically significant, relative risk of 1.57.

The hypothesis for the prognostic relevance of random biopsies is that concomitant dysplastic changes reflect a premalignant state of the entire urothelial surface which is prone to developing new tumour occurrences and muscle invasion. Poor prognostic ability does not necessarily mean that this hypothesis is false. In theory, a high predictive ability of mucosal abnormalities may be obscured by low accuracy and poor reproducibility in the interpretation of biopsy specimens. In a study by the Medical Research Council it was shown that the reproducibility in the interpretation of random biopsies was very poor.[37] Unfortunately, it is not possible to separate the biological behaviour of dysplastic urothelium areas (the real prognostic potential) from the inaccuracy in the interpretation of random biopsies. The prognostic ability of random biopsies may improve, therefore, with more objective criteria for morphological abnormalities,[37] or with alternative methods of interpretation, such as DNA flow cytometry.[33]

4. In primary superficial bladder cancer, no definite consensus has been reached yet on treatment policy. Even though, because of the strong correlation between dysplastic changes in normal-looking urothelium and other prognostic factors, it is likely that most of the patients with dysplastic urothelium would have been treated adjuvantly anyway (e.g., patients with a grade 3 tumour). Thus, for most patients with concomitant mucosal abnormalities, this finding is irrelevant for the choice of treatment.

5. If the primary interest in a prognostic factor is optimization of treatment management then this prognostic factor will be fairly insignificant with low treatment efficacy. The efficacy of intravesical therapy in primary superficial bladder cancer is no longer doubted regarding the prevention of new occurrences. However, it remains to be proven regarding the risk of progression.

The purpose of our study was to examine the rationale of routine quadrant biopsies of normal-looking urothelium in primary superficial bladder cancer. We used decision-analytical methods in order to be able to take all the aforementioned factors into account. Based on the data from a large unselected prospective series of newly diagnosed superficial bladder cancer patients, we found that there is little reason to take random urothelium biopsies at initial endoscopical surgery. If random biopsies are taken from all the patients, then the 3-year risk of recurrence decreases by only 2%. The 3-year risk of progression does not change at all. In sensitivity analyses we tested the stability of this conclusion by using findings from the literature on the prevalence of dysplastic abnormalities in patients with low grade tumours, and on the prophylactic effect of intravesical instillations with chemotherapy or BCG. Furthermore, we assumed a fairly extreme independent prognostic effect of the presence of dysplasia or CIS in normal-looking urothelium when the RR was considered to be 3.0 for both the risk of recurrence and the risk of progression. This RR would mean that in a hypothetical population with a certain prognostic profile, a 3-year risk of recurrence of 50% would increase to 87% in the case of concomitant urothelial abnormalities. An assumed 3-year risk of progression of 15% would change to 39%. Despite all these assumptions we found that the ultimate benefit of random biopsies remained limited. Compared to the no-biopsy policy, the 3-year risks of recurrence and progression were reduced by no more than 5% and 4%, respectively, whereas an extra 31% of patients with primary disease would have to be treated with intravesical instillations.

In our opinion, this extra proportion of patients who would have to be treated with intravesical therapy, and as such would experience discomfort to varying degrees, is the major disadvantageous effect of the use of random biopsies as an additional prognostic test. Although rarely fatal, side-effects of intravesically instilled agents are quite common.[24] The second (less important) disadvantage of taking random biopsies as an additional prognostic test is the direct and indirect financial cost. The direct cost relates to the histopathological interpretation of extra biopsy specimens. The indirect cost results from the application of intravesical instillations to more patients. To some extent, however, the financial cost will be compensated for by saving some patients from having to undergo one or more endoscopic resections (or more aggressive treatment).

As aforementioned, no definite consensus has yet been reached on the clinical management of patients with superficial bladder cancer. In our 'no-biopsy policy' we defined a conservative treatment policy (except for the patients with a pT1G3 tumour, all the patients were treated with TUR alone) in order to evaluate the maximum possible benefit of the alternative 'biopsy policy'. Urologists may not agree with these (simplified) policies. Alternative policies are those in which random biopsies are applied more selectively The urologist does not know the histopathology result of the resected tumour (stage and grade) before he has to decide whether or not to take random biopsies From the prior endoscopy, however, he will know the size and multicentricity of the tumour. Thus, an alternative policy may be to treat all the patients with multiple tumours with intravesical chemotherapy and to take random biopsies only from the patients with solitary tumours. We evaluated this 'alternative biopsy' strategy with the same decision-tree we used before (see Figure 8 1), by applying it to patients with a solitary tumour only (70% of all the 1745 patients with superficial TCC in our case series). Using the same assumptions as we did before, the 3-year risks of recurrence and progression in the no-biopsy policy were 59% and 11%, respectively. In the biopsy policy these risks were 53% and 9%, respectively Thus, the beneficial effect of routine random biopsies remained disappointing.

We conclude that there is no good reason to take routine random biopsies of normal-looking urothelium in patients with newly diagnosed superficial bladder cancer. The ultimate benefit of taking random biopsies is only a slight decrease in the risks of recurrence and progression (even if optimal conditions are assumed) at the expense of a substantial increase in the number of patients who would have to be treated with adjuvant intravesical instillations

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CHAPTER 9

PROGNOSTIC ASSESSMENT FROM STUDIES WITH NON-RANDOMIZED TREATMENT ASSIGNMENT

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SUMMARY

In clinical practice, prognostic factors are primarily used to identify and select patients with a relatively poor prognosis who may need more aggressive treatment in order to improve their prognosis. Preferably, assessment of the ability of prognostic factors to distinguish these high risk patients from low risk patients should take place in the absence of such prognosis-modifying adjuvant therapy. Adjuvant therapy may dilute the effect of prognosticators (covariate-treatment interactions) and such a situation may go unnoticed in tests for interaction because of their low statistical power. Therefore, for the evaluation of prognostic factors, it is argued that the study population should be restricted to patients who do not receive adjuvant therapy. This restriction might result in a less powerful analysis, but it carries the advantage that undetectable biases are avoided. Non-random treatment assignment will not invalidate this restricted analysis provided that all the prognostic factors on which treatment choice was based, are known and incorporated into the analysis.

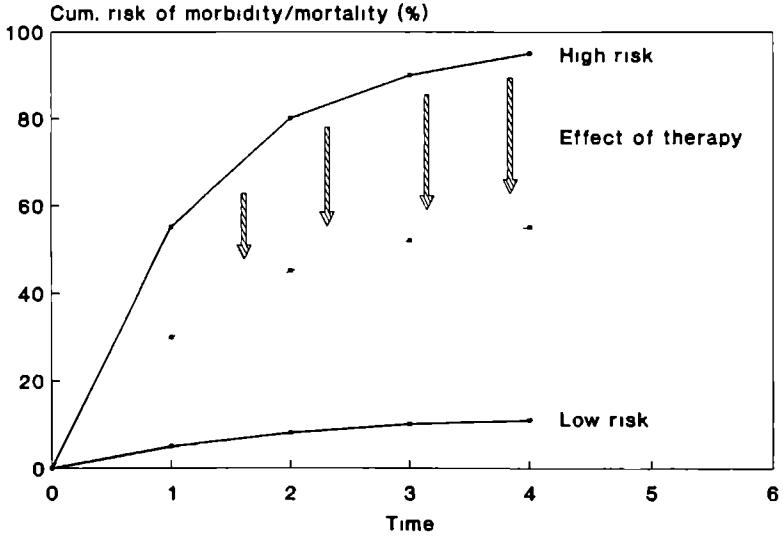
INTRODUCTION

The aim of prognostic assessment is to identify a set of covariates (or 'prognostic factors'), which in combination will enable the optimal discrimination of patients with a poor prognosis from those with a favourable prognosis. Prognostic factors do not necessarily have any direct causal relationship with the outcome of a disease. For example, in low-stage cancer where it is believed that the tumour has been completely removed by 'curative' surgery, the tumour itself can no longer influence the prognosis, but the tumour's characteristics may still form useful prognostic factors. However, in addition to *prediction*, a second goal of prognostic assessment is *elucidation* or *explanation* (like in aetiological research). Knowledge of prognostic factors which have a direct causal relationship with disease outcome, facilitates the understanding of the pathophysiology of the disease and may direct specific interventions. For example, even though 'yellow stained fingers' may have predictive ability for myocardial infarction in patients with coronary artery disease, knowing that smoking is the real causal factor means a step forward in the understanding and management of the disease. In this paper, we consider both aspects of prognostic assessment to be important and assume that every (prognostic) factor has a certain, yet to be identified, quantitative effect on prognosis.

In clinical practice, prognostic factors are primarily used to optimize treatment policies. A fairly conservative treatment (or none at all) may suffice for a group of patients with a relatively good prognosis, whereas a more aggressive treatment may be required for patients with a relatively poor prognosis (Figure 9.1). With this in mind, it seems trivial to say that

prognostic assessment should take place in the absence of the more aggressive treatment modality. If a group of patients receive (adjuvant) therapy, prognostic factors will not necessarily explain the 'natural history' of the disease in the absence of this (adjuvant) therapy, but they may predict the disease course under the influence of interactions between the treatment and the disease itself.[1,2] This means that in a treated population, the potential importance of a new prognostic test may have been masked (or amplified) by treatment. For example, in low-stage bladder cancer, adjuvant intravesical chemotherapy may be administered after endoscopical resection of the tumour(s), in order to prevent recurrences. The presence of concomitant dysplastic lesions in biopsy specimens from the cystoscopically normal-looking urothelium might aid in the selection of patients who need such intravesical chemotherapy. Evaluation of the prognostic value of concomitant dysplasia in patients who were treated adjuvantly may be impossible, however, because the chemotherapy will have 'modified' the urothelium.

FIGURE 9.1 *Prognostically high and low risk patients with intended modification of the prognosis by (adjuvant) treatment for high risk patients*



From sheer necessity, prognostic tests are frequently evaluated in cohorts of patients which contain various proportions of different treatment modalities. One fairly standard approach for prognostic assessment on the basis of the

data from these studies with randomized or non-randomized treatment assignment, is to fit a model using the full data set and then to assume that the effects of the prognosticators are the same in different treatment arms and to augment this assumption with tests for interaction. However, tests for interaction often have little statistical power, so that a non-significant result may not rule out clinically important differences in effects. In this paper, it is argued that a restricted data set (containing a particular treatment group) should be used for prognostic factor analyses instead of the full data set, even if treatment has been applied in a non-randomized fashion.

DESIGN OF PROGNOSTIC FACTOR STUDIES

Notation (Holland and Rubin, 1988)[3]

Consider a population of patients with some disease for which two treatment modalities k exist; k=c is some kind of standard therapy (or no therapy at all in some diseases) routinely administered to all patients (c='control'); k=e is an optional adjuvant therapy from which patients may benefit at the expense of potential side-effects (e='extra'). A response Y is recorded for each patient after exposure to one of the two modalities k: Y=0 is still alive after time t; Y=1 is death before t. Formally, instead of a single dependent variable Y we have a dependent variable Y_k for each of the treatments to which a patient could have been exposed. If the patient had been exposed to treatment c, the value Y_c would have been recorded for that patient. If that same patient had been exposed to treatment e, then the value Y_e would have been recorded. Thus, the following vector is associated with each patient:

(1) (Y_e, Y_c),

where Y_k is the patient's response after exposure to treatment k.
Although formally each patient has a value for both Y_e and Y_c, a patient is exposed to only one of the two treatments k and therefore, we observe only Y_e or Y_c. In order to relate the vector in (1) to the data which are actually observed, the variable S is introduced, where S=k if the patient is treated with k; S is the variable which indicates the k assigned to each patient. The observed data from a patient is the vector

(2) (Y_s, S).

The notation Y_s is used because it indicates that we can observe only the response of a patient to the treatment to which he/she was exposed, that is

(3) $Y_s=Y_k$ if S=k, for k=c and k=e

The response Y not only depends on k, but it also depends on the patient himself. Subgroups of patients can be defined by the value of a covariate X or a vector of covariates **X**. The interest in treatment efficacy studies lie in k, whereas the interest in prognostic assessment lies in **X**.

Prognostic assessment

As aforementioned, in addition to prediction itself (what to tell the patient about his or her future), for clinical practice the interest in the covariates **X** will lie in the treatment policy (what to do for the patient).[4] Especially in diseases such as cancer where intended effects of treatment may go hand in hand with considerable side-effects, the underlying motive for a prognostic factor study is usually improvement of the clinician's ability to discern patients who should receive adjuvant treatment k=e from those who should not (although a high failure rate may not be synonymous with a high responsiveness to k=e). With such a motive, the optimal design of the study is simple: select a population of patients with the disease of interest, do not intervene with k=e and observe the realisation of Y_c in subgroups with different host and/or disease characteristics **X**.

Studies are seldom initiated, however, strictly because one is interested in prognostic factors. Frequently, prognostic factor analyses are carried out using data from a randomized controlled trial. If data are only used from the control arm (k=c), the prognostic factor study will still have an optimal design (although specific eligibility criteria for a trial may affect the generalizability of the results). In Table 9.1 the results of a hypothetical large trial are summarized. Fifty per cent of all the patients were treated with the standard treatment k=c after randomized assignment. Using the data from this trial, a particular covariate X_j, an ordinal factor with 3 levels (low, intermediate and high), was evaluated for its prognostic significance. Logistic regression modelling of the data in Table 9.1 as observed among patients treated with k=c, yielded an odds ratio (OR) of 4.1 (95% CI: 1.8-9.3) for X_j = intermediate vs. X_j = low. For X_j = high vs. X_j = low, OR=7.9 (95% CI: 3.6-17.5). (For reasons of notational simplicity, the time at which death occurred was not considered.) Below, we assume that these ORs are the 'real' quantitative effects of X_j.

NO RESTRICTION OF THE POPULATION

With regard to the identification of prognosticators to be used in treatment management, we are not really interested in the prognostic effect of X_j in patients who have already received adjuvant treatment k=e. Nevertheless, using all the patients in the analysis would yield a narrower confidence interval around the estimated effect of X_j.

TABLE 9.1 *Results of a hypothetical randomized clinical trial*

Covariate X_j	k=c (standard therapy)			
	Dead ($Y_c=1$)	Alive ($Y_c=0$)	Total	$Pr(Y_c=1 \mid S=c)$
Low	9	91	100	0.09
Intermediate	29	71	100	0.29
High	44	56	100	0.44
Total	82	218	300	0.27

Covariate X_j	k=e (adjuvant therapy)			
	Dead ($Y_e=1$)	Alive ($Y_e=0$)	Total	$Pr(Y_e=1 \mid S=e)$
Low	5	95	100	0.05
Intermediate	17	83	100	0 17
High	29	71	100	0.29
Total	51	249	300	0.17

Logistic regression analysis on both the left hand side and the right hand side data in Table 9.1 (all k), resulted in $OR_{Intermediate\ vs\ Low}=4.0$ (95% CI: 2.1-7.6) and $OR_{High\ vs\ Low}=7.9$ (95% CI: 4.2-14.7). (For k=e vs. k=c, OR=0.5; 95% CI: 0.3-0.8). The width of the confidence intervals shows that the statistical power of the study did increase when all the patients were included. However, this analysis is only valid in situations where there is no interaction between k and X_j, as was the case in our hypothetical trial. The ORs for $X_j=x_j$ in the group of patients treated with k=e and the group treated with k=c were the same. A test for interaction produced a likelihood ratio statistic (Chi^2_{LR}) with 2 degrees of freedom (df) of 0.01 (p=0.99).

Let us now assume a hypothetical trial with treatment-covariate interaction (see Table 9.2). It can be seen that k=e did not have any effect on the low risk group, whereas k=e almost halved the chance of dying in the high risk group. Nevertheless, the test for interaction was not significant in this reasonably large trial with 600 patients: $Chi^2_{LR}=2.60$ with df=2: p=0.27. If we were to specify a model without interaction terms in addition to X_j and K, however, this would result in 'biased' ORs. Naturally, we wanted to find $OR_{Intermediate\ vs\ Low}=4.1$ and $OR_{High\ vs\ Low}=7.9$ (because the data in the left hand side of the table did not change), but the analysis resulted in OR=3.3 and

OR=5.3, respectively. Unbiased ORs were obtained while maintaining the interaction terms in the model, even though these terms were not statistically significant. In that case, the ORs were 4.1 (95% CI: 1.8-9.3) and 7.9 (95% CI: 3.6-17.5). Note that the confidence intervals are exactly the same as those in the situation where we restricted the analysis to the standard therapy group k=c. This is not very surprising because the model was saturated by the incorporation of all the possible interaction factors in the model. Thus, in the case of treatment-covariate interactions, including all the patients in the analysis does not increase the power of the study.

TABLE 9.2 *Results of a hypothetical randomized clinical trial with treatment-covariate interaction*

Covariate X_j	**k=c (standard therapy)**			
	Dead ($Y_c=1$)	Alive ($Y_c=0$)	Total	$Pr(Y_c=1 \mid S=c)$
Low	9	91	100	0.09
Intermediate	29	71	100	0.29
High	44	56	100	0.44
Total	82	218	300	0.27

Covariate X_j	**k=e (adjuvant therapy)**			
	Dead ($Y_e=1$)	Alive ($Y_e=0$)	Total	$Pr(Y_e=1 \mid S=e)$
Low	9	91	100	0.09
Intermediate	20	80	100	0.20
High	24	76	100	0.24
Total	53	247	300	0.18

In real life, the situation will not be as simple as in our trial. There may be a large number of covariates **X** with covariate-covariate interactions, which may also interact with k. In this case, the analysis as well as the interpretation of the results will become fairly complicated. In our opinion, therefore, it is preferable to restrict the analysis to k=c, except in the (utopical) situation in which one is absolutely certain that there are no treatment-covariate interactions.

THE USUAL DESIGN OF A PROGNOSTIC FACTOR STUDY

Data from a randomized trial may not always be available or suitable to be used for prognostic factor analyses, for instance, because some covariate X_j of interest was not part of the study protocol. It is sometimes possible to perform a prognostic factor study on data from a patient series which has already been documented for other purposes. Very often, part of such a series will have been assigned to some kind of adjuvant therapy k=e in a non-randomized fashion. **How does this non-randomized treatment assignment affect the results of the analysis?**

Let us assume that in a hypothetical patient series, X_j is the only host or disease characteristic which influenced treatment assignment. Most of the patients with a low score on X_j were treated conservatively with k=c, whereas most of the patients with a high score on X_j were treated with k=e. The fact that not all the patients with X_j=low were treated with k=c and not all the patients with X_j=high were treated with k=e, is the result of some patients' and some physicians' preferences (not related to prognosis) for one of the two modalities. If we further assume the same treatment-covariate interaction as was illustrated in Table 9.2, this would lead to the data presented in Table 9.3. Because treatment assignment is based on X_j only, for each $X_j=x_j$, $Pr(Y_c=1 \mid S=c)$ and $Pr(Y_e=1 \mid S=e)$ are the same as in the randomized trial of Table 9.2. However, owing to the non-randomized assignment, 121 patients would die in this series compared to 135 in the trial of Table 9.2.

Analysis of the left hand side data in Table 9.3 (k=c) yielded the following results: $OR_{\text{Intermediate vs. Low}}=4.2$ (95% CI: 2.1-8.4) and $OR_{\text{High vs Low}}=7.9$ (95% CI: 3.2-19.4). The similarity with the results from the aforementioned trial is not surprising, because for every X_j, $Pr(Y_c=1 \mid S=c)$ remained constant. An analysis without any restriction on k=c showed that the power of tests for treatment-covariate interactions was even lower than it was in the randomized trial situation: $Chi^2_{LR}=1.60$ (df=2: p=0.45). When treatment-covariate interactions were not included in the model using the full data set, the estimated prognostic effects were even more biased than in the randomized trial situation. For example: where the real $OR_{\text{High vs. Intermediate}}=1.9$, this OR was estimated to be 1.6 (95% CI:1.0-2.5) in the randomized trial situation (Table 9.2) and 1.4 (95% CI: 0.9-2.3) in the non-randomized situation (Table 9.3).

Thus, in the case of a single prognostic covariate, valid results can be obtained from a prognostic factor analysis on studies with non-randomized treatment assignment, as long as the analysis is restricted to k=c (or alternatively, as long as all possible treatment-covariate interactions are included in the regression model, whether statistically significant or not).

TABLE 9.3 *Results of a hypothetical non-randomized patient series with treatment-covariate interaction*

Covariate X_j	**k=c (standard therapy)**			
	Dead ($Y_c=1$)	Alive ($Y_c=0$)	Total	$Pr(Y_c=1 \mid S=c)$
Low	15	155	170	0.09
Intermediate	29	71	100	0.29
High	13	17	30	0.44
Total	57	243	300	0.19

Covariate X_j	**k=e (adjuvant therapy)**			
	Dead ($Y_e=1$)	Alive ($Y_e=0$)	Total	$Pr(Y_e=1 \mid S=e)$
Low	3	27	30	0.09
Intermediate	20	80	100	0.20
High	41	129	170	0.24
Total	64	236	300	0.21

NECESSARY CONDITION

The single covariate situation presented above can be generalized to the situation where treatment assignment is based on a vector of covariates. As long as this vector **X** is known, valid estimates of the prognostic effects of **X** (and other covariates) can still be obtained if the study population is restricted to the standard treatment group k=c when **X** is taken into account. In the non-randomized situation, $Pr(Y_s=1 \mid S=c, \mathbf{X})$ is equal to $Pr(Y_c=1 \mid \mathbf{X})$ regardless of the dependence between treatment assignment S and **X**. This can be expressed as follows.

The probability that some endpoint Y_s will be observed, given the assigned treatment S=k and covariates **X**, is

(4) $\quad Pr(Y_s=y \mid S=k, \mathbf{X}=x) \quad =$

$$\frac{Pr(Y_k=y\ ,\ S=k,\ \mathbf{X}=x)}{Pr(S=k,\ \mathbf{X}=x)} =$$

$$\frac{Pr(Y_k=y,\ S=k,\ \mathbf{X}=x)\ /\ Pr(\mathbf{X}=x)}{Pr(S=k,\ \mathbf{X}=x)\ /\ Pr(\mathbf{X}=x)} =$$

$$(5) \qquad \frac{Pr(Y_k=y,\ S=k \mid \mathbf{X}=x)}{Pr(S=k \mid \mathbf{X}=x)}$$

If all **X** which influenced the treatment assignment S (and may have influenced Y_k) are known and included in the model, then $Pr(Y_k=y \mid \mathbf{X}=x)$ and $Pr(S=k \mid \mathbf{X}=x)$ are independent and (5) is equivalent to:

$$\frac{Pr(Y_k=y \mid \mathbf{X}=x) * Pr(S=k \mid \mathbf{X}=x)}{Pr(S=k \mid \mathbf{X}=x)} =$$

$$(6) \qquad Pr(Y_k=y \mid \mathbf{X}=x) \qquad \text{for } k=c \text{ and } k=e$$

Note from (6) that treatment assignment S disappeared from (4). This does not mean that treatment itself is not important for a patient's prognosis. It only means that the estimated prognostic effects of **X** after restriction of the analysis to k=c will not be biased by treatment assignment. The necessary condition, therefore, is the incorporation of all covariates **X** which influenced both the treatment assignment and had an independent prognostic effect on Y_k. This condition has been defined by Rosenbaum and Rubin as *strongly ignorable treatment assignment* in their work on causal inference from non-randomized studies.[5,6] Treatment assignment (i.e., the distribution of S, given **X** and Y_k) is *strongly ignorable* if:

(a) given **X**, S is independent of Y_k for all k, and
(b) $Pr(S=k \mid \mathbf{X}=x) > 0$ for all k.

In Table 9.3, we assumed that for every X_j the conditional probabilities $Pr(Y_c=1 \mid S=c)$ were similar to those in the randomized trial situation. If the condition of strongly ignorable treatment assignment is not met, then $Pr(Y_c=1 \mid S=c)$ for each X_j in Table 9.3 is dependent on some unknown factor and biased estimates of $OR_{\text{Intermediate vs. Low}}$ and $OR_{\text{High vs Low}}$ will be obtained.

DISCUSSION

In studies on treatment efficacy, one of the basic validity issues is the physician's reasoning in deciding how to treat a patient. Although this decision is primarily based on the patient's prognostic profile, it can be fairly complex and difficult to quantify. Therefore, differences in outcomes between treated and control groups may not reflect the effects of the treatment, but rather pretreatment differences which may not have been measured. To overcome this, Rosenbaum[7-9] and Rosenbaum and Rubin[5,6,10-12] have repeatedly advocated the use of a scalar function of covariates (the so-called 'propensity score') to balance covariates, in order to obtain strongly-ignorable treatment assignment in observational studies. This condition of strong ignorability is less restrictive than that of randomization and the plausibility of assuming that the condition holds true needs to be considered carefully in any real application.[3] (For a more detailed discussion of the evaluation of strongly ignorable treatment assignment, see Rosenbaum and Rubin[5] and Rosenbaum[7]). Although the use of the propensity score may suffice in most instances, there will always be the possibility that the estimated efficacy of some therapy has been biased by some unmeasured covariate. From a theoretical point of view, this makes it impossible to study intended therapy effects using non-randomized studies.[13]

In our opinion, the role of randomization in prognostic assessment is not entirely comparable to its role in treatment efficacy assessment. If we wished to compare the efficacy of k=e to that of k=c in a particular population, some difficult-to-measure covariates in this population may be important for treatment assignment and may also influence the prognosis Y_k. An example of these covariates is comorbidity. To achieve comparability ('internal validity') of the treatment group and control group, k must be assigned at random. In theory, the possible confounding effect of comorbidity will be prevented by this randomization. If the primary interest is not treatment efficacy but the prognostic effects of covariates **X**, these effects would have to be adjusted for the prognostic effect of comorbidity, at least if the emphasis lies in causal relationships between covariates and the prognosis (i.e. *elucidation*). However, whether or not the study was randomized, we do not have access to data on comorbidity. The only thing we do know is that unmeasured factors will be equally distributed over the treatment arms in the case of a randomized trial. Although this may facilitate the generalizability of the results of prognostic assessment using data from the control arm of a trial, it will still be impossible to assess the 'real' quantitative effects of **X** (adjusted for comorbidity).

A problem which may result from restricting the analysis to one treatment group in an observational study, is that of statistical power. In a randomized study population, prognostic characteristics will be balanced over the treatment groups. In a non-randomized study, there will be different distributions of prognostic characteristics over the various treatment groups. The patient group that has been treated with the least intensive regimen probably contain relatively more patients with a favorable prognosis. In our hypothetical

example presented in Table 9.3, most of the patients with X_j = high had been given k=e. There may be situations in which all of these patients were treated with k=e, so it will be impossible to study the prognostic value of X_j = high in k=c. This extreme situation is reflected in one of the conditions of strongly ignorable treatment assignment: $Pr(S=k \mid X=x) > 0$ for all k. If this condition is met, then the ability to assess the prognostic value of a new test (whether or not in specific prognostic subgroups) is a matter of power rather than of validity. In other words, the problem does not lie in the fact that the patient group treated with k=c was selected, but in the size of this selected group.

The application of treatment as a prognostic factor to solve this potential power problem is a very appealing approach, because it is not necessary to restrict the study population, so all the prognostic subgroups will be represented in the analysis. However, treatment itself may affect the estimated quantitative value of prognostic factors. As was shown above, significance tests can be used to check for the existence of interaction, but the lack of power of these tests may lead to biased estimates and possibly to wrong conclusions. Moreover, if one insists on doing tests, the logical choice is an equivalence test rather than a significance test.[14] Restricting the group of patients to those who really are of interest (patients who were treated with k=c only), however, is much easier. Furthermore, in situations where most patients with a certain prognostic profile were treated adjuvantly, such a restriction carries the advantage that therapy does not obscure any lack of power to assess the prognostic effect of some factor.

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CHAPTER 10

GENERAL DISCUSSION

The core of this thesis was based on data from the "Documentation project bladder cancer" which was initiated by urologists, pathologists and radiotherapists from the areas of the Comprehensive Cancer Centres IKO, IKZ and IKA-ST. In this chapter, the background of the project is described, as well as its shortcomings with regard to conducting scientific research using the available data. The major results of the studies presented in this thesis are summarized and leads are proposed for future research in superficial bladder cancer.

BACKGROUND

Superficial bladder cancer is a disease with a relatively short 'history'. Not so long ago, a large proportion of superficial bladder tumours were designated benign papilloma and were therefore not considered to be cancer.[1] During the 1970s, papillary-shaped non-invasive tumours became increasingly defined as carcinoma. Nowadays, these non-invasive tumours comprise approximately 70% of superficial bladder carcinomas and approximately 45% of all bladder carcinomas. In urological practice, a clear distinction is made between patients with superficial disease and patients with invasive disease because of differences in prognosis and management. Most cancer registries and epidemiological studies on bladder cancer have not (yet) made such a distinction.[2-3] Precise data on the occurrence and etiology of superficial bladder cancer is therefore relatively scarce.

In contrast, much clinical research has already been conducted into the prognosis of patients with superficial transitional cell carcinoma (TCC) of the bladder. Overall figures for the risk of recurrence, risk of progression and mortality are available, although these figures are frequently based on more or less selective and small patient series. As a consequence, this research has not yet resulted in clinicians being able to make fairly accurate predictions of disease outcome in superficial TCC. The disease encompasses a spectrum that ranges from innocuous to life-threatening lesions, which are difficult to distinguish.[4]

The same holds true for the treatment management of patients with superficial TCC. Quite a number of clinical trials have shown that the intravesical administration of chemotherapeutical agents inhibits recurrent tumour formation, but the effect of these agents on disease progression is still uncertain.[5] Increasing evidence has suggested that BCG immunotherapy, unlike chemotherapy, can alter the natural history of superficial bladder cancer by providing long-term protection against tumour recurrence, by reducing the incidence of stage progression and by reducing disease mortality, but the available data are still limited.[6] Inaccurate prognostication as well as ineffective prevention of disease progression are the primary reasons for the

relative absence of consensus regarding the management of patients with primary superficial TCC.

BLADDER CANCER DOCUMENTATION PROJECT

In order to gain an insight into the clinical management of patients with bladder cancer and to facilitate the comparison of treatment results with data from the literature, a "Documentation project bladder cancer" was initiated by urologists, radiotherapists, pathologists and oncologists in the south-eastern part of the Netherlands, who were also collaborating in the Comprehensive Cancer Centre IKO "Working Group Urological Oncology". The aim of this project was defined as "... to collect data on the character and extent of disease in patients with primary bladder cancer; to gain an insight into the epidemiology of the disease; and to evaluate the results of treatment".[7] As an integral part of the documentation project a booklet "Guidelines for the treatment of bladder cancer" was prepared and distributed among the project's participants.[8]

In 1982, a population-based cancer registry which could serve as a primary source and framework for the documentation project, was not yet in operation. For that reason, all the data in the project were documented by the participating urologists and radiotherapists. A data manager was appointed to collect the data. The decision as to whether or not a patient should be documented, was made by the treating urologist.

From the start of the project, several research questions were of interest to the participants in the project, although they had not been formally operationalized. With respect to the group of patients with superficial bladder cancer, these research objectives were related to the ability of predicting disease outcome in individual patients and the rationale of taking cold-cup mucosal biopsies for prognostication and (subsequent) treatment management.[9] Most of the contents of this thesis concern the evaluation of the latter research questions.

THE PROJECT'S DRAWBACKS

Initially, the project was not set up with the aim of carrying out scientific research, but of carrying out applied research. Furthermore, as mentioned above, the research questions were not clearly defined at the very beginning of the project. Both of these factors led to a number of difficulties.

The treatment guidelines

The major difficulty with the analysis of the documented data was related to the treatment guidelines themselves. It was advised to treat patients with a

primary solitary superficial (pTa and pT1, Nx M0) tumour with transurethral resection (TUR) only. In the case of multiple primary tumours, the advised policy was TUR, if necessary in combination with intracavitary chemotherapy. In the case of a primary pT1G3 tumour with a diameter of less than 5 cm, it was advised to consider interstitial radiotherapy (radium, caesium) after preoperative external 3 x 3.5 Gy radiotherapy. Thus, except for a solitary grade 1 or 2 tumour, more than one treatment option was listed for all the tumours. Moreover, if it was decided to administer intracavitary chemotherapy, the urologist could choose from four agents: thiotepa, doxorubicin (Adriamycin), cisplatin or ethoglucid (Epodyl).

After the start of the project, many papers appeared in the scientific literature on the efficacy (and side-effects) of these and other agents (mitomycin-C, Bacillus Calmette-Guérin) which once more influenced the treatment policy of the participating urologists. All this resulted in a lack of uniformity of treatment policy. Quite a number of patients with a primary solitary grade 1 tumour were treated with adjuvant intravesical instillations (27%), whereas a surprisingly high percentage of patients with pT1G3 tumours were treated with TUR only (26%).

Treatment assignment

This non-randomized treatment assignment as well as the diversity of agents, made it impossible to evaluate treatment effectiveness. We wondered, however, in what way the application of therapy in a non-randomized fashion may have affected the results of the prognostic factor analyses. In superficial bladder cancer, there are no uniformly accepted indications for the administration of intravesical therapy.[10] In our project, the most important factor for treatment assignment appeared to be a factor which was not related to the patient's prognosis, *i.e.* the urologist's (and the patient's) preference: some urologists administered intravesical instillations to almost all their patients, whereas others hardly ever did. Other factors which were important for treatment assignment were age, tumour stage, grade, multiplicity, size and concomitant intraurothelial dysplastic changes. Owing to the availability of information about all these factors, it was possible to make adjustments for treatment assignment in order to obtain valid results in the prognostic factor analysis.[11] A factor which may have influenced treatment policy in some patients but was not measured in the project, is comorbidity (unrelated to superficial bladder cancer). However, we assumed that comorbidity could not have influenced the two endpoints in our study: recurrence and progression.

Low statistical power

The primary topic of interest was to evaluate the ability of prognosticators to identify and select patients with a relatively poor prognosis who might benefit from adjuvant intravesical instillations. For this purpose, we wanted to aim the study at patients who had not received these instillations, but due to the non-randomized treatment assignment, some prognostic subgroups of patients were

underrepresented in the TUR only group. For example, only 10 of 86 patients with carcinoma in situ (CIS) in the cystoscopically normal-looking urothelium of 1044 patients, were treated with TUR only. The statistical power to evaluate the prognostic effect of CIS in this group of patients was therefore extremely low.

Data collection

Another difficulty was related to the compilation of data by the participating urologists and radiotherapists. Despite their enthousiastic participation throughout the years, they appeared not to be professional 'data managers'. Data collection was stopped in July 1991 and the documented data of almost 2000 patients with pTa, pT1 or pTis were checked for validity using the medical files. It was found that 85 patients (4%) had recurrent disease or cancer of the upper urinary tract at first registration instead of a primary bladder cancer. Errors were made with the registration of tumour stage, tumour grade, the result of random biopsies and the treatment applied in 146 (7%), 91 (5%), 259 (13%) and 38 (2%) records, respectively. We were able to solve this problem by checking all the records. Where necessary, correction of the data was carried out and the records of 100 patients were deleted.

Item list

Owing to the fact that some research questions were not formulated until after the project had started, a number of relevant items were missing from the documentation protocol. Several of these items, such as tumour multiplicity at first diagnosis and disease progression during follow-up, could be collected retrospectively. Unfortunately, it was not feasible to collect all the potentially relevant information, which meant that only incomplete data could be analysed for the following items: the specific chemotherapeutical or immunotherapeutical agent administered after initial TUR and subsequent TURs (for recurrences), the multiplicity of recurrences, the exact localisations of recurrences and the cause of death.

Review pathology

Tumour stage, tumour grade and the result of random urothelial biopsies were based on local pathology reports. Only the histological material of patients who were entered in a randomized trial and the histological slides of patients with a pT1G3 tumour were reviewed by one pathologist. The absence of review pathology in the majority of patients in the project rendered the project (in the terminology of Schwartz and Lellouch)[12] 'pragmatic' instead of 'explanatory'. It reflects everyday practice rather than a purely scientific situation under optimal conditions. Prognostic factors, such as tumour stage and grade, may have gained prognostic significance if a reference pathologist had been able to improve the distinction between Ta and T1 tumours and between low and high grade tumours, thereby reducing possible misclassification by the local pathologist. On the other hand, the benefit of

involving a reference pathologist in a study on prognostic factors is not as self-evident as it is in a study on treatment efficacy. Not only the generalizability of the results of a study may be decreased, but also a reference pathologist may not be the gold standard that we might think he is. For example, two reproducibility studies showed poor consistency in the grading of bladder tumours and the interpretation of random bladder biopsies by a number of experienced reference pathologists.[13 14] Thus, a reference pathologist may introduce systematic misclassification of the histopathology and bias the results of a prognostic factor analysis in an unpredictable direction.

Patient accrual

Patients were entered into the documentation project prospectively. Therefore, at the time of entry, there were no follow-up data. However, the project was not population-based, because the urologists decided whether or not to document a patient, which could have resulted in a selected patient series. Therefore, we compared the distribution of age, sex, tumour stage, grade and morphology in the documentation project to that in the population-based IKO cancer registry. Fortunately, no differences were observed in the distribution of these characteristics. The documentation project appeared to reflect everyday clinical practice, as it was meant to do.

RESULTS

As listed in Chapter 1, the aims of this thesis "Prognostic assessment in superficial bladder cancer" were:

- to study trends in bladder cancer occurrence and mortality in the Netherlands;
- to study the prognostic significance of concomitant intraurothelial dysplastic lesions (detected by means of random urothelium biopsies) for recurrent tumour formation and disease progression in primary superficial bladder cancer;
- to quantify the predictive power of the available set of prognostic factors in primary superficial bladder cancer; and
- to evaluate the rationale of the implementation of random urothelium biopsies in the management of patients with primary superficial bladder cancer.

The most important findings were as follows.

- Bladder cancer mortality in males was still seen to be increasing in 1988. Because the risk of dying from bladder cancer appeared to decrease in successive birth cohorts born after 1910, mortality in males will probably decline in the near future. Bladder cancer mortality rates in females were fairly stable between 1955 and 1988 (Chapter 2).
- Over the past two decades, a dramatic increase has been observed in the occurrence of bladder cancer. This increase was caused almost entirely by

changes in the classification of low-grade non-invasive bladder tumours. From 1975 onwards, the occurrence of invasive bladder cancer has increased only slightly. In more recent years, no clear trend has been observed towards lower disease stages and better survival (Chapter 3).

- The 5-year risk of recurrent disease in patients with primary superficial bladder cancer was approximately 60%. The 5-year risk of progression was estimated to be 13%. Considering this risk of progression, quite surprisingly the 5-year relative survival was calculated to be approximately 86% (Chapter 4).
- The risk of recurrence in patients with dysplasia or CIS in macroscopically normal-looking urothelium was only slightly higher than the risk in patients without any dysplastic changes. In addition to other prognostic factors, concomitant dysplastic changes significantly increased the risk of progression (Chapter 6).
- Prediction of recurrent tumour formation and disease progression in patients with primary superficial bladder cancer on the basis of tumour stage, grade size, multicentricity and the result of random urothelium biopsies, was only accurate on average in whole patient groups. Predictions of these disease outcomes in individuals were found to be highly inaccurate (Chapter 7).
- The implementation of random urothelium biopsies in the management of patients with primary superficial bladder cancer does not lead to any noteworthy decrease in the risks of recurrence and progression, whereas a considerable number of extra patients will be treated with adjuvant intravesical instillations on the basis of positive biopsy results (Chapter 8).

LEADS FOR FUTURE RESEARCH

Histopathology

Histopathological characteristics are very important in the management of patients with superficial bladder cancer. However, the reproducibility of histopathology, especially the tumour's degree of differentiation, is still poor.[13] A great deal of research is ongoing into quantitative methods in urological oncology. These quantitative methods may result in more reproducible (and valid) histology reports and improve their prognostic value. But until more standardized automated fixation, embedding, staining, selection and measuring techniques become available, quantitative light microscopy cannot be applied as a routine tool for prognostic assessment, although it may play an important role in the comparison of subsequent samples in patient follow-up.[15]

Molecular biology

Superficial bladder cancer encompasses a heterogeneous group of tumors whose neoplastic features differ markedly. The true biological potential of these tumours is determined by their genetic blueprint. Tumour stage and grade are manifestations of these genotypes. Until now, cytogenetic studies

and Restriction-Fragment-Length Polymorphism (RFLP) analyses have shown that chromosomal changes (*e.g.* allelic losses, variation in chromosome number and aneuploidy) are associated with a loss of cell differentiation. Marker chromosomes are associated with an increased risk of recurrence and progression. Non-random abnormalities have been found on chromosomes 1, 3, 5, 7, 9, 11 and 17. Especially deletions of chromosomes 11p and 17p are believed to be relevant in tumour progression.[16] Mutations in the p53 gene on 17p are associated with tumour progression (not only in bladder cancer, but in many other cancers).[17-18] Many tumour markers are correlated with tumour stage and grade, but the biological significance (regarding the patients' clinical course) of a number of these markers remains unclear.[19] Recently, the decreased expression of E-cadherin, an intercellular adhesion molecule, has been found to be associated with poor survival in patients with bladder cancer.[20] Further progress in the field of molecular biology and studies on the clinical relevance of tumour markers may facilitate the more accurate identification of patients with a high risk of tumour progression and death from bladder cancer.

The 'malignant' bladder

It has been recognized for some time that in (at least) a proportion of all the patients with superficial bladder cancer, the tumours are manifestations of cystoscopically occult widespread disease. Such 'field change defects' can be detected by taking random biopsy specimens from normal-looking urothelium and examining them for morphological dysplastic lesions. However, the prognostic significance of dysplastic changes, if present, appears to be limited. For this reason, prognostic research into superficial bladder cancer still focusses on the characteristics of the resected tumour(s). But this research identifies the malignant tumour rather than the extent to which the remaining bladder mucosa is potentially 'malignant'. Despite the fact that the resected tumour may form an indirect indicator of a patient's prognosis, it is the remaining bladder mucosa which will give rise to new, possibly invasive, tumour occurrences. Sharper focus on the remaining bladder mucosa to identify yet unknown cellular changes may help to detect the patients who truly run a significant risk for progression. If better cytological evaluation methods become available, random biopsies may ultimately prove to be a useful procedure for prognostic assessment.

Recurrence

More adequate definitions of disease outcome are required. In our project for example, the time to first recurrence (or 'risk of recurrence') was analysed. A considerable number of patients, however, suffered one (or a few) occasional recurrence(s) without any real malignant potential. In clinical practice, such a patient will be managed quite differently from a patient who suffers multiple recurrences within a short period of time. For this reason, some studies used the 'recurrence rate' as an endpoint instead of 'risk of recurrence'. The

recurrence rate is defined as the number of follow-up cystoscopies at which a recurrence is detected, divided by the total number of months of follow-up.[21] A clear disadvantage of this measure is that patients are not considered as independent observations: one patient with five positive follow-up cystoscopies is equivalent to five patients with one positive cystoscopy. It may be possible to define a new endpoint which incorporates both the time to recurrence and multiplicity (*e.g.* time to multiple recurrences either diagnosed in one cystoscopy session or in two successive cystoscopies). Such an alternative endpoint may create more sensitive circumstances for the identification of prognostic factors.

Progression

Progression, a shift to a higher tumour stage category or the development of regional or distant metastases, the other endpoint in superficial bladder cancer, also deserves some further attention. In our study, we found that the 5-year relative survival in superficial bladder cancer was approximately 86%. This finding is consistent with other reports.[22-24] The 5-year risk of progression was found to be only 13%. This finding is consistent with the overall risk of progression found by the U.S.A. National Bladder Cancer Collaborative Group.[4] Per definition, in superficial bladder cancer, bladder-cancer-related death is only possible after disease progression. Furthermore, not all the patients who suffer disease progression will die from bladder cancer. It may be wondered, therefore, why we found an excess risk of dying from bladder cancer, which was very similar to the risk of progression. One fairly theoretical explanation is that bladder-cancer-related death was overestimated by calculating the relative survival because of bias from comorbidity-related death. Another possible explanation is that bladder cancer death (because of disease progression) was misclassified as non-bladder-cancer-related death in some of the patients.

Treatment management

More research is necessary in order to specify the optimal treatment management of patients with superficial bladder cancer. Firstly, recent studies have revealed that incomplete transurethral resection (TUR) occurs more frequently than was previously believed in patients with T1G3 tumours. Approximately 60% of all the patients suffered tumour recurrence at the same site in a study by Jakse and associates.[25] Klan and colleagues found residual tumour with an early second resection of the same site in 40%.[26] Possibly, the techniques of TUR need to be improved. Secondly, controversy exists regarding not only the ideal agent to administer for intravesical instillations, but also the ideal regimen.[27] The primary focus of such research must be disease progression.[28] Currently, the available chemotherapeutical agents have not proven to be effective in preventing progression. Recently, some promising results have been reported with BCG.[6,29,30] Hopefully, ongoing research to evaluate the sequential combination of intravesical chemotherapy

using mitomycin-C and intravesical immunotherapy with BCG (University Hospital Nijmegen protocol no. 911201) will add to these promising results.

Methodology of prognostic assessment

Although patient management is strongly individualized in clinical practice, the results from research into prognostic assessment are seldom translated in terms of individual patients. More specifically, the ability to distinguish between patients who will have a positive disease outcome and those who will have a negative disease outcome has rarely been quantified. However, quantification of this discrimination ability is no easy task and suitable methods are still lacking. In our study, we used a method which is comparable to the construction and interpretation of Receiver Operating Characteristic (ROC) curves in diagnostic assessment.[31] With this method, an index of concordance 'c' is calculated by comparing the observed and predicted disease outcomes within all possible pairs of patients. For any given pair, we say that the predictions are concordant with the outcomes if the patient with the higher probability estimate of (let us say) survival, lived longer. If both patients are still alive, or if only one has died and the follow-up of the other is shorter than the survival time of the first, we do not count that pair. The 'c' index is the proportion of all the pairs of patients for which we could determine the order of survival such that the predictions were concordant. This index is a linear transformation of a Kendall-Goodman-Kruskal type correlation between a set of predicted probabilities and the true outcomes.[32] The major advantage of 'c' is that it is easy to interpret because it estimates the probability that for a pair of patients chosen at random, the one with the longer predicted survival is the one who will survive longer. However, there are some clear disadvantages. Firstly, in clinical practice, a physician is confronted with just one patient rather than a pair chosen at random. Secondly, as explained above, a number of pairs cannot be counted in the calculation of 'c' because of censoring. Therefore, research is ongoing in the field of medical statistics to design more suitable measures. Korn and Simon have recently advocated the use of measures of explained variation for survival data based on loss functions (analogous to R^2 in the analysis of variance).[33] These measures do not have the disadvantages of the measures based on rank correlations, such as 'c'. However, the interpretation of the measures is more difficult and different loss functions lead to different results. Thus, hopefully sooner or later, more research in this field will result in an optimal measure for discrimination ability (or synonymously: predictive power).

Cancer registry

Finally, the role of Dutch regional cancer registries (held by the Comprehensive Cancer Centres) in projects such as the bladder cancer documentation project, deserves some emphasis. As aforementioned, the bladder cancer documentation project could not make use yet of the infrastructure of the cancer registry. Nowadays, the cancer registry can

provide the following facilities: a population-based documentation of patients with some kind of cancer; professional registrars who know their way around every hospital in the Netherlands and are trained to collect data according to strictly defined rules; high quality facilities for data storage and analysis which comply with the existing confidentiality legislations, and professional methodological expertise to assist with the design and execution of studies. Furthermore, the initiation of documentation projects is an area of special attention in the Comprehensive Cancer Centres' policies. Therefore, the Comprehensive Cancer Centres may serve as a fruitful platform for interaction between oncology, clinical epidemiology and medical technology assessment outside the boundaries of university hospitals.

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SUMMARY

Almost 6 per cent of all primary cancers are located in the urinary bladder. Among the 15 million inhabitants of the Netherlands, approximately 3400 new cases of bladder cancer are diagnosed each year, with a strong male predominance. Bladder cancer is the third most frequently occurring tumour in men, after lung cancer and prostate cancer. In the Netherlands, approximately 1100 Dutch men and women die from the disease each year. (*Chapter 1*)

According to data from the Dutch Central Bureau of Statistics, there has been an increasing trend in bladder cancer mortality in Dutch men since the 1950s. In 1955, only 350 bladder cancer deaths were registered. After adjusting for the ageing of the Dutch population in the past decades, male mortality rates were found to have increased from 7.5 per 10^5 person-years in the period 1955-1959 to 12.4 per 10^5 person-years in the period 1985-1988. In contrast, female mortality rates per 10^5 person-years were found to have hardly increased from 2.9 in the first to 3.0 in the latter calendar period, indicating the absence of any temporal trend in females. Statistical modelling of male mortality rates from 1955 to 1988 by age, calendar period and birth cohort, showed that the observed rates can be described adequately by a so-called age-cohort model. This means that the increasing temporal trend can be explained by a changing risk of dying from bladder cancer in successive birth cohorts, instead of a changing risk in successive calendar periods. It was found that the risk of dying from bladder cancer increased from the 1875 birth cohort to the 1910 birth cohort, but decreased thereafter. For example, compared to men born in 1910, the calculated risk of bladder cancer death for men (of the same age) born in 1940 was 67%. There may have been a calendar period effect as well, but this was found to be quantitatively negligable. The lower risk for generations born after 1910 has not yet resulted in a decreasing trend in bladder cancer mortality rates in the Netherlands. Possibly, such a decline will be observed within the next decade when more cohorts with a relatively low risk reach high risk ages. This would correspond with the sharp fall in the proportion of smokers among Dutch males from 90% in the late 1950s to 40% in the 1980s, as smoking is believed to be the most important aetiological factor in bladder cancer. (*Chapter 2*)

In most Western communities, increasing trends in bladder cancer incidence can be observed which are comparable with the increasing trend in mortality. However, these increasing trends do not necessarily reflect increasing risks of developing bladder cancer. Changes in the classification and reporting of low-stage and low-grade papillocarcinomas may have resulted in biased trends in time of bladder cancer incidence as well as bladder cancer survival. Using data from the population-based Eindhoven cancer registry, it was found that age-adjusted male bladder cancer incidence per 10^5 person-years rose from 25.9 in 1975 to 40.7 in 1989. Female incidence rose from 3.1 to 8.5. These increases in incidence were probably almost entirely caused by the introduction of a new grading system in 1973 and a new staging system in

1978. These new classification systems resulted in the registration of non-invasive pTa papillary carcinomas, formerly classified as 'benign' or 'borderline' papillomas. Taking this alteration in classification into account, there has been only a small increase in the occurrence of bladder cancer in females. No clear shift towards lower disease stages and lower fatality rates have been observed during the past two decades. (*Chapter 3*)

In urology, non-invasive pTa papillary carcinomas, relatively rare flat carcinomas in situ (pTis) and tumours which invade the lamina propria of the bladder wall (pT1), are defined as superficial bladder cancers. Although the majority of patients with primary bladder cancer initially present with a solitary or multiple superficial tumour(s), quantitative knowledge of disease characteristics of superficial bladder cancer is fairly scarce. Using data from a documentation project in the south-eastern part of the Netherlands, it was found that 65% (N=1745) of all primary bladder cancers were diagnosed with stage pTa or pT1 transitional cell carcinoma (52 patients or 2% had primary pTis). Of all the patients with pTa/pT1 cancer, 81% were men. The median age at diagnosis was 67 years both in males and females. Haematuria was the main first symptom in more than 80% of all the patients. In 32% of all the patients a pT1 tumour was diagnosed, 16% had a grade 3 tumour and 29% had multiple tumours at first presentation. All these percentages were higher in patients who were older at diagnosis. Within 3 years after the diagnosis, more than 50% of all the patients suffered at least one recurrence. Patients with a recurrence were prone to having more recurrences. In 10% of all the patients, tumour progression was observed within 3 years. Both the risk of recurrence and the risk of progression strongly depended on the aforementioned tumour characteristics. The calculated 5-year relative survival of patients with superficial bladder cancer was 86%. (*Chapter 4*)

Despite the prognostic ability of, *e.g.*, tumour stage, grade and multiplicity, it is the urologist's experience that the outcome of disease in patients with superficial bladder cancer is difficult to predict. Therefore, a great deal of research is ongoing into the identification of additional prognostic factors for tumour recurrence, tumour progression and bladder cancer death. The literature was reviewed to make an inventory of the available evidence of the prognostic ability of clinical factors, histopathological factors, blood group antigens, cytogenetic factors, biochemical factors and tumour-associated antigens. Recurrence rate before and after treatment, cystoscopic features, such as tumour multiplicity and size, and the histopathological characteristics (tumour stage and grade) appeared to be the most important prognosticators. The value of blood group antigens is controversial. DNA ploidy and chromosomal aberrations are promising factors but further studies are necessary to establish the exact biological role of most of the observed aberrations. Cell motility, extracellular matrix degradation and the epidermal growth factor receptor are also promising factors. Although some monoclonal

antibodies (*e.g.*, Mab T138) were shown to have prognostic ability for tumour progression, it is not yet known which antigen changes in neoplastic cells are causally related to tumour progression. The significance of any new prognostic factor additional to the clinical and histopathological characteristics used in clinical practice until now, remains to be proven. (*Chapter 5*)

A factor which is believed to have such additional meaning is the presence of concomitant dysplastic lesions diagnosed with random biopsies from the cystoscopically normal-looking urothelium. In the bladder cancer documentation project (described in *Chapter 4*) random biopsies were taken from the 'normal' bladder mucosa in 1044 patients. In 22% of these patients, dysplasia (13.6%) or carcinoma in situ (8.2%) was found. The calculated 3-year actuarial risk of recurrence in patients with such dysplastic lesions was 57%, whereas this risk was 51% in patients without dysplastic lesions ($P=0.09$). In patients with and without dysplastic lesions, the calculated 3-year risk of tumour progression was 21% and 7%, respectively ($P<0.001$). After adjusting for the effects of the routinely used prognostic factors by means of a proportional hazards model, the result of random biopsies was not found to have any prognostic significance regarding the risk of recurrence, but the presence of concomitant intraurothelial dysplastic lesions increased the risk of progression by a factor of 1.8 (90% CI: 1.3-2.5). Although the interacting effect of adjuvant intravesical chemotherapy instillations was accounted for in the analyses, the therapy applied may have obscured the real prognostic ability of concomitant dysplasia to some extent. (*Chapter 6*)

In clinical practice, prognostic factors are primarily used to optimize the management of individual patients. In superficial bladder cancer, the ability to predict the disease outcome on the basis of the available prognostic factors has never been quantified. Using a random 50% sample of the patients registered in the documentation project, prognostic index scores were constructed for the risks of recurrence and progression. The prognostic indices were based on tumour stage, extent, grade, multiplicity and the result of random biopsies. Patients with a low prognostic index score were predicted to have a 44% chance of having a recurrence within 3 years and a 3% chance of tumour progression within 3 years. These predicted risks for patients with a high score were 74% and 22%, respectively. The predicted risks were found to be fairly reliable when compared to the observed risks of recurrence and progression among the remaining 50% of the patients. However, the predictive accuracy of the prognostic indices for disease outcome in individual patients was disappointing. In any two patients chosen at random, the chance that the patient with the worst predicted prognosis would have a shorter recurrence-free and progression-free follow-up interval, was calculated to be only 58% and 67%, respectively. Thus, the use of prognostic factors for the prediction of disease outcome in individuals, is not much better than the flip of a coin. (*Chapter 7*)

Although the presence of concomitant urothelial dysplastic lesions was shown to have prognostic value for the risk of tumour progression in patients with primary superficial bladder cancer (*Chapter 6*), this does not necessarily mean that it is worthwhile to implement taking random biopsies in everyday urological practice. Apart from financial cost considerations, the rationale of taking biopsies also depends on, *e.g.* the number of patients with dysplastic abnormalities, the extent to which these biopsies can differentiate high risk from low risk patients, the number of patients who would have been treated adjuvantly anyway and the efficacy of adjuvant therapy. By means of decision analysis, it was attempted to take all these relevant factors into account. Comparing a hypothetical patient management policy in which random biopsies were taken from all the patients, to a policy in which random biopsies were not taken, showed that the 3-year risks of recurrence and progression were almost identical with both policies. Under very optimistic assumptions regarding the aforementioned factors which favour the policy of taking random biopsies, sensitivity analyses revealed that the risks of recurrence and progression could be reduced by 5% and 4%, respectively. In that case, however, 43% instead of 12% of all the patients would have been treated with intravesical instillations. It was concluded that there is no good reason to take routine random biopsies. (*Chapter 8*)

Prognostic factors are primarily used to discern high risk patients who need a more aggressive treatment regimen from low risk patients for whom more conservative management may suffice. Therefore, prognostic assessment studies should preferably take place in the absence of such prognosis-modifying adjuvant therapy. Adjuvant therapy may obscure the potential effect of prognostic factors because of treatment-covariate interactions which may be difficult to identify in the analysis. If prognostic factor analyses are carried out using patient series in which adjuvant therapy was administered to a proportion of the patients, it is argued that the analysis should be restricted to the patients who did not receive adjuvant therapy. The statistical power of this restricted analysis may be lower, but undetectable biases are avoided. It was shown that non-random treatment assignment does not invalidate the results of the restricted analysis as long as all the prognostic factors on which treatment choice was based, are known and are incorporated into the analysis. With this condition, a situation is achieved which is defined as 'strongly ignorable treatment assignment' in the statistical literature. (*Chapter 9*)

A large part of the research presented in this thesis was based on data from the "Documentation project bladder cancer". As this project was not initiated to carry out scientific research, some methodological problems were encountered in the analysis of the data. These problems are discussed in the final chapter of this thesis. Furthermore, some leads for future research into superficial bladder cancer are proposed. (*Chapter 10*)

SAMENVATTING

Bijna 6% van alle primaire maligniteiten is gelokaliseerd in de urineblaas. Onder de 15 miljoen inwoners van Nederland worden elk jaar ongeveer 3400 nieuwe patiënten gediagnostiseerd. De meeste patiënten zijn van het mannelijk geslacht.

Bij mannen is blaaskanker na longkanker en prostaatkanker de meest voorkomende vorm van kanker. In Nederland sterven elk jaar ongeveer 1100 mannen en vrouwen aan blaaskanker. (*Hoofdstuk 1*)

Volgens gegevens van het Centraal Bureau voor de Statistiek bestaat er sinds de vijftiger jaren een stijgende trend in blaaskankersterfte. In 1955 werden slechts 350 overlijdens aan blaaskanker geregistreerd tegenover het huidige jaarlijkse cijfer van 1100. Na correctie voor het effect van vergrijzing in de laatste decennia blijken de sterftecijfers onder mannen te zijn gestegen van 7,5 per 10^5 persoonjaren in 1955-1959 tot 12,4 per 10^5 persoonjaren in de periode 1985-1988. De sterftecijfers onder vrouwen bleven daarentegen vrij constant: 2,9 per 10^5 persoonjaren in de eerste ten opzichte van 3,0 per 10^5 persoonjaren in de laatste kalenderperiode. Bij statistische modellering van de sterftecijfers bij mannen van 1955 tot 1988 met parameters voor leeftijd, kalenderperiode en geboortecohort, bleek dat de geobserveerde cijfers adequaat kunnen worden beschreven door een leeftijd-cohort model. Een kalenderperiode-effect bleek verwaarloosbaar klein te zijn. Dit betekent dat de stijgende trend in sterfte beter verklaard zou kunnen worden door een veranderend risico om aan blaaskanker te overlijden in opeenvolgende geboortecohorten dan een veranderend risico in opeenvolgende kalenderperioden. Het risico nam toe vanaf het geboortecohort 1875 tot aan het cohort 1910, maar nam weer af voor jongere cohorten. Bijvoorbeeld: het risico op blaaskankersterfte voor mannen geboren rond 1940 was 67% van het risico voor mannen (van dezelfde leeftijd) geboren rond 1910. Dit lagere risico voor jongere generaties heeft nog niet geresulteerd in een dalende trend in blaaskankersterfte. Het is waarschijnlijk dat een dalende trend zich de komende jaren zal inzetten wanneer meer geboortecohorten met een relatief laag risico hogere (risico) leeftijden bereiken. Dit zou overeenkomen met de sterke daling in het percentage rokers onder de Nederlandse mannelijke bevolking van 90% in de vijftiger jaren naar 40% in de tachtiger jaren. Immers, roken wordt geacht de belangrijkste risicofactor van blaaskanker te zijn. (*Hoofdstuk 2*)

In de meeste Westerse landen worden ook stijgende trends gezien in de incidentie van blaaskanker. Deze stijgende trends worden echter niet noodzakelijkerwijs veroorzaakt door een stijgend risico op het krijgen van blaaskanker. Met name veranderingen in de klassificatie en rapportage van het laag-stadium en laag-gradig papillocarcinoom hebben mogelijk geresulteerd in vertekende trends in zowel incidentie als overleving van het blaascarcinoom. Met behulp van gegevens van de IKZ-SOOZ kankerregistratie werd berekend dat de voor leeftijdsopbouw gecorrigeerde incidentiecijfers per 10^5

persoonjaren bij mannen zijn gestegen van 25,9 in 1975 tot 40,7 in 1989. De incidentiecijfers bij vrouwen stegen van 3,1 tot 8,5. Waarschijnlijk werd de stijging in incidentie vrijwel geheel veroorzaakt door de introdukties van een nieuw graderingssysteem in 1973 en een nieuwe klassificatie van ziektestadium in 1978. Deze nieuwe klassificaties resulteerden in de registratie van het niet invasieve papillaire pTa blaascarcinoom, voordien geklassificeerd als "onrustig" papilloom. Wanneer rekening wordt gehouden met de veranderingen in klassificatie blijkt er slechts sprake te zijn van een zeer geringe stijging van de incidentie bij vrouwen. Bovendien blijkt er in dat geval in de laatste decennia geen duidelijke verschuiving te zijn opgetreden naar een lager ziektestadium en betere overleving. (*Hoofdstuk 3*)

Het niet invasieve papillaire pTa blaascarcinoom, het relatief zeldzame primaire carcinoom in situ (pTis) en de tumoren die slechts invasie vertonen in de lamina propria (pT1) worden in de urologie gedefiniëerd als oppervlakkig blaascarcinoom. Ofschoon de meeste blaaskankerpatiënten zich primair presenteren met een solitair of multipel oppervlakkig carcinoom zijn er weinig kwantitatieve gegevens beschikbaar over de ziektekarakteristieken. Uit gegevens van het Documentatieproject Blaascarcinoom, een gezamenlijk project van IKO, IKZ en IKA-Stedendriehoek/Twente, bleek dat 65% (N=1745) van alle patiënten met een primair blaascarcinoom gediagnostiseerd werd met een stadium pTa of pT1 overgangscelcarcinoom (52 patiënten, ofwel 2%, werd gediagnostiseerd met primair pTis). 81% van alle pTa/pT1 patiënten was van het mannelijk geslacht. De mediane leeftijd bij diagnose bij zowel mannen als vrouwen was 67 jaar. Haematurie was het belangrijkste eerste symptoom bij meer dan 80% van alle patiënten. Bij 32% van de patiënten was er sprake van een pT1 carcinoom, 16% had een graad 3 tumor en 29% van alle patiënten werd gediagnostiseerd met multipele tumoren. Al deze percentages waren hoger bij patiënten met een hogere leeftijd bij diagnose. Binnen 3 jaar na de diagnose werd bij meer dan 50% van alle patiënten minstens één recidief gediagnostiseerd. Patiënten met een recidief hadden een relatief hogere kans om nog meer recidieven te krijgen. Tumorprogressie binnen 3 jaar werd gezien bij 10% van alle patiënten. Zowel het risico op een recidief als het risico op tumorprogressie was afhankelijk van de bovengenoemde tumorkarakteristieken. De 5-jaars relatieve overleving van patiënten met een oppervlakkig blaascarcinoom was 86%. (*Hoofdstuk 4*)

Ondanks de prognostische betekenis van bijvoorbeeld tumorstadium, graad en multipliciteit heeft de uroloog de ervaring dat het ziekteverloop bij patiënten met een oppervlakkig blaascarcinoom moeilijk te voorspellen is. Daarom vindt er veel onderzoek plaats naar additionele prognostische factoren voor recidivering, progressie en blaaskankersterfte. In de literatuur werd gezocht naar beschikbare gegevens over de prognostische waarde van klinische factoren, histopathologische factoren, bloedgroepantigenen, cytogenetische factoren, biochemische factoren en tumor-geassocieerde antigenen.

Cystoscopische karakteristieken zoals tumormultipliciteit en grootte en de histopathologische factoren stadium en graad blijken de meest belangrijke prognostische factoren te zijn. Het optreden van recidieven is prognostisch voor frequente recidivering en progressie. De waarde van bloedgroepantigenen is controversiëel. DNA ploïdie en een aantal specifieke chromosoom-afwijkingen zijn veelbelovende factoren maar de precieze biologische betekenis van de meeste van deze afwijkingen moet nog worden onderzocht. Celmotiliteit, extracellulaire matrix degradatie en de EGF-receptor zijn eveneens mogelijke prognostische factoren. Hoewel de prognostische waarde voor tumorprogressie werd aangetoond van sommige monoclonale antilichamen (bijvoorbeeld Mab T138) is het nog niet bekend welke veranderingen in antigenen in neoplastische cellen causaal gerelateerd zijn aan tumorprogressie. De additionele betekenis van welke factor dan ook naast de al bekende klinische en histopathologische factoren moet nog worden aangetoond. (*Hoofdstuk 5*)

Een factor waarvoor een dergelijke additionele prognostische betekenis wordt vermoed is de aanwezigheid van dysplastische laesies in het macroscopisch normaal ogend blaasslijmvlies. In het Documentatieproject Blaascarcinoom (*Hoofdstuk 4*) werden random biopsieën van het 'normale' urotheel genomen bij 1044 patiënten. Bij 22% van deze patiënten werd dysplasie (13,6%) of carcinoma in situ (8,2%) gevonden. Het 3-jaars actuariële risico op recidief bij patiënten met dergelijke dysplastische laesies was 57%. Het risico bij patiënten zonder dysplastische laesies was 51% (P=0,09). Het 3-jaars risico op tumorprogressie bij patiënten met en zonder dysplastische laesies was respectievelijk 21% en 7% (P<0,001). Na correctie voor het effect van de standaard prognostische factoren met behulp van het proportional hazards model, had het resultaat van random biopsieën geen additionele prognostische betekenis meer voor recidivering. Echter, het risico op progressie werd verhoogd met een factor 1,8 (95% BI: 1,3-2,5) bij aanwezigheid van dysplasie of CIS. Hoewel werd getracht om het mogelijk verstorende effect van adjuvante chemotherapie instillaties te corrigeren in de analyse is het mogelijk dat chemotherapie het werkelijke prognostische effect van dysplastische laesies in 'normaal' urotheel heeft vertroebeld. (*Hoofdstuk 6*)

In de klinische praktijk zijn prognostische factoren met name van belang om het behandelingsbeleid te optimaliseren voor elke individuele patiënt. Bij het oppervlakkig blaascarcinoom is de mogelijkheid om het verloop van de ziekte te voorspellen op basis van de beschikbare prognostische factoren echter nog nooit gekwantificeerd. Met behulp van de gegevens van een 50% random steekproef van de patiënten in het documentatieproject werden prognostische indices geconstrueerd voor het risico op recidief en progressie. De indices werden gebaseerd op tumorstadium, uitbreiding, graad, multipliciteit en het resultaat van random biopsieën. Voor patiënten met een lage prognostische index score werd een 3-jaars risico op recidief voorspeld van 44% terwijl een

3-jaars risico op progressie werd voorspeld van 3%. De voorspelde risico's voor patiënten met een hoge score waren respectievelijk 74% en 22%. Bij vergelijking met de geobserveerde risico's op recidief en progressie bij de overige 50% van de patiënten in het project, bleken de voorspelde risico's vrij betrouwbaar te zijn. Echter, de nauwkeurigheid van voorspelling van het ziekteverloop bij individuele patiënten met behulp van de indices was teleurstellend. Er werd berekend dat voor elk random paar van patiënten, de kans dat de patiënt met de voorspelde slechtste prognose inderdaad een kortere recidiefvrije overleving heeft, maar 58% is. Deze kans is 67% voor progressievrije overleving. Voorspelling van het ziekteverloop bij de individuele patiënt met een primair oppervlakkig blaascarcinoom op basis van prognostische factoren is dus niet veel beter dan een pure gok. (*Hoofdstuk 7*)

Hoewel de aanwezigheid van dysplastische laesies in het normaal ogend urotheel prognostische waarde bleek te hebben voor het risico op progressie (*Hoofdstuk 6*), is de zin van het nemen van random biopsieën bij elke nieuwe patiënt niet vanzelfsprekend. Afgezien van een kostenaspect, is de potentiële waarde van random biopsieën afhankelijk van bijvoorbeeld het aantal patiënten met dysplastische laesies, de mate waarin de aanwezigheid van deze laesies een goede en slechte prognose kan onderscheiden, het aantal patiënten dat ook al adjuvant behandeld zou zijn wanneer geen dysplasie of CIS zou zijn ontdekt, en het effect van die adjuvante behandeling. Door middel van een besliskundige analyse werden deze factoren in beschouwing genomen. Wanneer een hypothetisch behandelingsbeleid dat (mede) gebaseerd is op het resultaat van random biopsieën vergeleken wordt met een beleid waarbij geen random biopten worden genomen blijken de 3-jaars risico's op recidief en progressie nagenoeg identiek te zijn bij beide vormen van beleid. Onder vrij extreme aannames met betrekking tot de hiervoor genoemde factoren, allen het beleid van het nemen van random biopten bevoordelend, werd met behulp van een sensitiviteitsanalyse aangetoond dat het risico op recidief en progressie respectievelijk 5% en 4% lager wordt met het nemen van random biopsieën. In dat geval wordt echter 43% van de patiënten behandeld met adjuvante chemotherapie tegen 12% wanneer geen random biopsieën worden genomen. Geconcludeerd werd dat het weinig zin heeft om random biopsieën te nemen bij alle nieuwe patiënten met een oppervlakkig blaascarcinoom. (*Hoofdstuk 8*)

Prognostische factoren worden voornamelijk gebruikt om patiënten met een relatief slechte prognose te onderscheiden van patiënten met een relatief goede prognose. Voor de eerste groep is mogelijk een (meer agressieve) adjuvante behandeling noodzakelijk terwijl voor de tweede groep een min of meer conservatieve behandeling zou kunnen volstaan. Studies naar prognostische factoren vinden daarom bij voorkeur plaats in afwezigheid van een dergelijke prognose-modificerende adjuvante behandeling. Immers, adjuvante behandeling kan het potentiële effect van prognostische factoren maskeren door interacties tussen die factoren en behandeling, terwijl het aantonen van

dergelijke interacties in de analyse zeer moeilijk is. In het geval dat een studie naar prognostische factoren plaatsvindt met gegevens van patiënten waarvan een gedeelte adjuvant werd behandeld, is het aan te raden de analyse te beperken tot de conservatief behandelde patiënten. De power van zo'n 'restrictie-analyse' is mogelijk lager, maar niet-detecteerbare vertekening door toegepaste therapie wordt voorkomen. Er werd aangetoond dat ook bij non-random behandelingstoekenning een restrictie-analyse leidt tot valide resultaten. Voorwaarde is wel dat alle factoren waarop de behandelingskeuze werd gebaseerd bekend zijn en worden opgenomen in de analyse. In dat geval is er sprake van een situatie die in de statistische literatuur wordt gedefiniëerd als "strongly ignorable treatment assignment". (*Hoofdstuk 9*)

Een groot gedeelte van dit proefschrift werd gebaseerd op de gegevens van het "Documentatieproject Blaascarcinoom". Omdat dit project niet primair werd opgezet met de bedoeling wetenschappelijk onderzoek te verrichten, bestonden er enige problemen bij de analyse van de gegevens. In het laatste hoofdstuk van dit proefschrift worden deze problemen besproken. In dat hoofdstuk worden ook aanbevelingen gedaan voor toekomstig onderzoek bij het oppervlakkig blaascarcinoom. (*Hoofdstuk 10*)

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Een gedeelte van dit proefschrift is gebaseerd op het Documentatieproject Blaascarcinoom. Alle deelnemers aan het project[@] wil ik bedanken voor hun inzet. Rie Speijers-van Doremalen en Marjorie de Kok verzamelden jarenlang nauwgezet de benodigde gegevens voor het project.
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En dan Claire Zonder jou

[@] De aan het project deelnemende urologen waren
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CURRICULUM VITAE

Bart Kiemeney werd geboren op 17 juli 1960 te Hilvarenbeek. In 1978 haalde hij het diploma Atheneum B aan het St. Odulphus Lyceum te Tilburg. In 1983 studeerde hij af als fysiotherapeut aan de Academie "West Brabant" te Breda. Na zijn militaire dienstplicht startte hij in 1984 met de nieuw ingerichte studie Gezondheidswetenschappen aan de Faculteit der Medische Wetenschappen van de Katholieke Universiteit Nijmegen (KUN). Als afstudeerrichting koos hij epidemiologie. Binnen deze afstudeerrichting liep hij stages bij het Centrum voor Klinische Besliskunde van de Erasmus Universiteit Rotterdam en de Vakgroep Medische Informatiekunde en Epidemiologie (MIE) van de KUN. Vanaf augustus 1988 werkte hij bij het Integraal Kankercentrum Oost (IKO) te Nijmegen als hoofd van de afdeling kankerregistratie. Door het IKO werd hij voor half-time als wetenschappelijk medewerker gedetacheerd bij de Vakgroep MIE voor een verdere opleiding in de epidemiologie (de kankerepidemiologie in het bijzonder) onder leiding van Prof. A.L.M. Verbeek. In oktober 1992 is hij gestart met een opleiding in de klinische en genetische epidemiologie in het kader van een 2-jarig fellowship dat werd toegekend door de Nederlandse Kankerbestrijding "Stichting Koningin Wilhelmina Fonds". Middels dit fellowship zal hij voor bepaalde tijd werkzaam zijn bij de afdeling Klinische Epidemiologie van het Academisch Ziekenhuis Leiden (Prof. J.P. Vandenbroucke), de afdeling Medische Statistiek van de Rijksuniversiteit Leiden (Prof. J.C. van Houwelingen), de Department of Epidemiology van de University of Washington, Seattle (Prof. N.S. Weiss) en de Department of Epidemiology van de Johns Hopkins University, Baltimore (Prof. T.H. Beaty). Tevens vervult hij sinds begin 1993 een functie als consulent epidemiologie bij het IKO.
Bart Kiemeney is getrouwd met Marie-Claire van der Steen. Samen hebben zij drie kinderen: Danique, Marenne en Jan.

IK/O

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Mocht u geïnteresseerd zijn in de mogelijkheden van de Kankerregistratie, neem dan contact op.

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STELLINGEN

behorende bij het proefschrift:

"Prognostic assessment in superficial bladder cancer"

Bart Kiemeney

Nijmegen, 29 juni 1993

1. De in Nederland nog steeds stijgende sterfte aan blaascarcinoom zal voor de eeuwwisseling gaan dalen. (Dit proefschrift)

2. De ogenschijnlijke toename in het optreden van (oppervlakkig) blaascarcinoom sinds 1975 is het gevolg van klassifikatieveranderingen. (Dit proefschrift)

3. Dysplastische laesies in normaal-ogend blaasslijmvlies bij patiënten met een oppervlakkig blaascarcinoom hebben enige additionele prognostische waarde voor tumorprogressie. (Dit proefschrift)

4. Een betrouwbare voorspelling van het ziekteverloop bij een patiënt met een primair oppervlakkig blaascarcinoom is op dit moment niet mogelijk. (Dit proefschrift)

5. Het nemen van random biopsieën van normaal-ogend blaasslijmvlies bij patiënten met een oppervlakkig blaascarcinoom heeft weinig zin. (Dit proefschrift)

6. De wijze van correctie voor de invloed van toegepaste therapie in studies naar prognostische factoren verdient methodologische aandacht. (Dit proefschrift)

7. De wereld wordt niet gekenmerkt door wat we zien, maar door wat we over het hoofd zien. (Jopie Huisman, 1992)

8. Als eis voor registratie tot epidemioloog ligt een gedegen mathematisch statistische kennis minstens zo voor de hand als een gedegen medische kennis.

9. Het aanhangen van de gedachte 'schoenmaker blijf bij je leest' is dodelijk voor de wetenschap.

10. Positieve discriminatie gaat per definitie gepaard met 'negatieve discriminatie' en is dus verwerpelijk.

11. Het gebruik van de term *ziektebeloop* in plaats van de juiste term *ziekteverloop*, is opmerkelijk daar in de kliniek weinig op zijn *beloop* wordt gelaten.

12. Beter tien vogels in de lucht dan één op het strand.